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REVIEW ARTICLE

A Comprehensive Review on the State of the Art of Breast Cancers in Italy

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Abstract: Breast cancer (BC) currently represents one of the most prevalent cancers among women worldwide and the leading cause of cancer death among women, also negatively affecting the quality of life (QoL) in patients. Over the past two decades, BC research has led to extraordinary advances in our understanding of the disease, resulting in more effective treatments. However, its occurrence is still increasing. Several new treatments are now under development worldwide, but they are not devoid of well-known side effects, and a great number of patients develop endocrine resistance. Nevertheless, the design and synthesis of more suitable strategies and new drugs to treat breast cancers, overcome resistance and side effects, and obtain better therapeutic outcomes are needed. In this review, we summarize the therapies and the clinical studies currently ongoing in Italy for the treatment of BCs, mainly $HER2^+$ MBC, HER2-low MBC, and TNBC, focusing on the most recent ones, also in consideration of diverse facets, including some aspects related to QoL. Finally, some studies related to the usefulness of physical activity in BC will be cited.

Keywords: Breast cancer, $HER2^+$ MBC, TNBC, HER2-low BCs, QoL, physical activity.

1. INTRODUCTION

Malignant tumors are currently the second leading cause of death in the world [1]. Among them, BC is the most usually diagnosed type of cancer and represents the main cause of cancer-related death in women. The most common therapies used for the treatment of BC have been recently reviewed in detail by our research group [2]. BCs are categorized on the basis of the receptors' expression, for instance, hormone receptors (HR), comprising estrogen receptor (ER) and progesterone receptor (PR), and human epidermal growth factor 2 receptor (HER2). They are classified into different categories, including HR-positive (HR^+) or -negative (HR^-)and/or HER2-enriched ($HER2^+$) or tumors that lack HER2 protein overexpression ($HER2^-$) cancers. Triple-negative BC (TNBC) is so called as it lacks the expression of the three molecular markers, namely ER, PR, and HER2: it represents the most aggressive form of BCs and accounts for 10-20% of all BCs worldwide. HR^+ cancers account for 70-80% of all breast cancers and are characterized by estrogen-dependent growth. $HER2^-$ cancers represent about 80% of BCs. Among them, BCs with a HER2 immunohistochemical (IHC) score of 1+ or 2+ with negative *in situ* hybridization are called HER2-low BCs and represent approximately 45-55% of BCs [3]. The knowledge of the biological and clinical features of this subtype of

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cancer is still limited and controversial [4, 5]. Conventional therapies play a major therapeutic value in BCs, both in the adjuvant and recurrent settings. However, a great number of patients show side effects even in years of follow-up after cure and/or develop endocrine resistance, which leads to tumor recurrence. Besides the common myelotoxicity evidenced by all the therapies, non-hematological toxicities, which are represented by mucositis oral, pneumonitis, dysphagia, esophagitis, nausea, vomiting, anorexia, malaise, diarrhea, enterocolitis, dermatitis, cystitis, cardiovascular adverse effects and so on, continue to affect anticancer therapies [6-11].

Moreover, BC represents a real disruption in terms of QoL-related aspects in patients' lives, such as the distortion of body image, the psychosocial consequences following the diagnosis, the effect on family dynamics, and so on [12]. The metastases of cancer cells from the primary tumor site to other organs in the body, notably the lungs, bones, brain, and liver, is what causes breast cancer to ultimately be fatal. Specifically, brain metastases occur in as many as 30% of patients with advanced BC, representing an awful event for patients, which affects their survival and QoL, leading to morbidity and mortality [13]. The 1-year survival rate of these patients is around 20% [14]. Thus, much more work and research need to be done in this field. Finally, it is noteworthy that in recent years, studies regarding the involvement of physical activity in BC have been rising. This review highlights the research studies carried out in Italy, showing a roundup of the therapies available for the treatment of BCs and the most recent studies carried out in diverse Italian hospitals, particularly focusing on $HER2^+$ MBC, HER2-low BC, and TNBC.

2. THERAPIES FOR BREAST CANCERS

Several therapies are used nowadays in Italy and worldwide for the treatment of BC based on the subtype of cancer [2]. Below, the most used therapies for $HER2^+$ MBC, TNBC, and HER2-low BCs are summarized (Table **1**).

2.1. Therapies for $HER2^+$ MBC

Several studies and reviews are addressed to $HER2^+$ MBC [15-17]. An overview of the common systemic therapies for the treatment of this disease has been recently reported by the group of Prof. Curigliano (Milano, Italy) [18]. Immunotherapy represents the first-line option for $HER2^+$ MBC [19]. Specifically, trastuzumab (Herceptin, F. Hoffmann-La Roche, Ltd; Genentech, Inc.) is a monoclonal antibody directed to the extracellular domain of HER2 [20]. It was the first drug approved as anti-HER2 targeted therapy and now stands for the standard of care for $HER2^+$ EBC or MBC patients. Pertuzumab (Perjeta, Hoffmann-La Roche, Ltd; Genentech) is a recombinant humanized monoclonal HER2-binding antibody that targets the HER2 extracellular dimerization domain (subdomain II). It does not bind the same site of trastuzumab but a different one and inhibits the ligand-dependent activation of the HER2 pathway by the blockade of dimerization of HER2 with HER3 and other HER family receptors. Trastuzumab and pertuzumab activate the immune system *via* antibody-dependent cell-mediated cytotoxicity. Pertuzumab was approved on June 8, 2012, by the Food and Drug Administration (FDA) as therapy for patients with $HER2^+$ MBC who had not received former treatment for metastatic disease, based on results from the Clinical Evaluation Of Pertuzumab And TRAstuzumab (CLEOPATRA) study evaluating docetaxel and trastuzumab with pertuzumab or placebo. On September 30, 2013, the FDA and the European Medicines Agency (EMA) granted pertuzumab accelerated approval for use in association with trastuzumab and docetaxel as neoadjuvant therapy for patients with $HER2^+$, locally advanced BC (LABC), IBC,

Table 1. Clinical studies for different types of breast cancers.

ClinicalTrials.gov Identifier	Name of the Study	City	Phase	Recruitment Status	Last Update Posted
NCT04134598	Exclusive Endocrine Therapy or Radiation therapy for Women Aged ≥70 Years Early Stage Breast Cancer (EUROPA)	Florence	Phase III	Recruiting	January 31, 2023
NCT04591431	The Rome Trial From Histology to Target: the Road to Personalize Target Therapy and Immunotherapy (ROME)	Rome	Phase II	Active, not recruiting	May 3, 2023
NCT01849133	Randomized Trial on Intraoperative Radiotherapy Full Dose *vs* External Radiotherapy (ELIOT)	European Institute of Oncology, Milan, Italy	Not applicable	Completed	May 8, 2013

or EBC (either greater than 2 cm or lymph node positive) [21, 22]. Second-line therapy is generally represented by antibody-drug conjugates (ADCs). Trastuzumab emtansine (T-DM1) is an ADC linking the anti-HER2 humanized monoclonal antibody trastuzumab to DM1, a cytotoxic microtubule inhibitor. T-DM1 has been demonstrated to confer survival benefits in previously treated MBC in the EMILIA and TH3RESA phase III trials [23, 24]. For the past 10 years, based on the results of these trials, T-DM1 was considered the best treatment alternative for patients whose disease had evolved after trastuzumab- and taxane-based treatment [25]. Fam-trastuzumab deruxtecan-nxki (T-DXd), an ADC with an inhibitor of topoisomerase I, is now considered the best second-line therapy for patients with HER2-positive MBC previously treated with taxane in association with trastuzumab (and usually plus pertuzumab) according to a randomized phase III study DESTINY-Breast03 study (NCT03529110) of patients pretreated with trastuzumab and taxane [26, 27]. It has demonstrated better activity compared to T-DM1. Tyrosine kinase inhibitors (TKIs), such as tucatinib and capecitabine, are often used in combination with trastuzumab or T-DXd in the second-line setting in selected patients who have developed brain metastases. When T-DXd is not available, T-DM1 is still the preferred second-line treatment alternative after progression during the treatment with a taxane and trastuzumab. Tucatinib, capecitabine, trastuzumab, T-DXd and T-DM1 are likely the most active individual treatment options in the third-line setting. Moreover, the use of T-DXd in patients with the involvement of the central nervous system (CNS) is under study in several clinical trials that are now ongoing (DEBBRAH, TUXEDO, DESTINY-Breast12). Moreover, the phase III MARIANNE study (NCT01120184) was designed to better investigate the efficacy and safety of T-DM1 in patients with $HER2^+$ advanced BC (ABC) not previously treated. In the study by Perez *et al.*, carried out also in Italy by the group of Pierfranco Conte (Department of Surgery, Oncology and Gastroenterology, University of Padova and Istituto Oncologico Veneto, Padova, Italy), it was shown that biomarkers involved in the HER2 pathway (HER2 and HER3 mRNA expression levels, *PIK3CA* mutation status, *PTEN* H-score and protein expression level, and tumor heterogeneity) were not predictive for the progression-free survival (PFS) when T-DM1 (with or without pertuzumab) was compared with trastuzumab plus taxane. Nevertheless, HER2 mRNA level and PIK3CA mutation status demonstrated prognostic value. Finally, other potential biomarkers, such as immune markers, are still under evaluation [28]. For third-line therapy, a large variety of drugs is currently available for patients with trastuzumab-pretreated, pertuzumab-pretreated, and antibody-drug conjugate-pretreated $HER2^+$ MBC. The multiple options include TKIs, monoclonal antibodies, antibody-drug conjugates and non-chemotherapy anti-HER2 therapy. TKIs include tucatinib, lapatinib, pyrotinib [29] and neratinib [30]. Among monoclonal antibodies, trastuzumab + chemotherapy and the recently approved margetuximab in association with chemotherapy represent the main options for the treatment of previously treated $HER2^+$ MBC. Margetuximab (MARGENZA™, margetuximab-cmkb) represents a second-generation anti-HER2 monoclonal antibody [31] and is a trastuzumab derivative fragment crystallizable-engineered antibody under study in the phase III SOPHIA trial (NCT02492711). Patients must have had progressive disease after two or more lines of prior ERBB2-targeted therapy, including pertuzumab, and 1 to 3 lines of nonhormonal metastatic BC therapy. PFS was enhanced with margetuximab, but no significant OS benefit was observed. Margetuximab, in combination with chemotherapy, showed an admissible tolerability profile that was usually comparable to that of trastuzumab plus chemotherapy. From an exploratory study, the PFS benefit was suggested to be restricted to patients bearing an F allele for the fragment crystallizable-gamma receptor IIIA gene [32]. Antibody-drug conjugates are mostly represented by T-DXd; finally, anti-HER2 therapy without chemotherapics is used for patients with $HR^+/HER2^+$ tumors and indolent disease (lapatinib or trastuzumab with hormonal therapy), or for patients with $HR^-/HER2^+$ tumors and indolent disease or for those who do not tolerate or do not want to receive chemotherapy ("biologics only") [33]. Moreover, after the expiration of the trastuzumab European patent and US patent in 2014 and 2019, respectively, numerous producers submitted applications for biosimilars of trastuzumab. Some of them were recognized as therapeutically equivalent substitutions capable of enhancing patient access. A recent study carried out in Italy (Naples) [34] evidenced that there was no difference between biosimilars and references in terms of adverse side effects. The real cost-saving of the first 2 years of the study was higher than €800,000 and was estimated to raise over time. So far, five biosimilars of trastuzumab have received authorization in Italy for the treatment of patients with $HER2^+$ EBC or MBC: Kanjinti® (Amgen, Thousand Oaks, CA, USA), Ontruzant® (MSD), Ogivri® (Mylan, Canonsburg, PA, USA), Herzuma® (Mundipharma, Hong Kong, China) and Trazimera® (Pfizer, New York, NY, USA) [35, 36].

2.2. Therapies for Triple Negative Breast Cancer

TNBC is sensitive to chemotherapy; thus, this treatment remains the standard of care. An update on first-line treatment for metastatic TNBC has been recently reviewed [37, 38]. Commonly used chemotherapic drugs include anthracycline (*e.g.*, DNA intercalating agent and topoisomerase II blocker doxorubicin), alkylating agents (*e.g.*, cyclophosphamide), an anti-microtubule agent belonging to taxanes, and the anti-metabolite fluorouracil (5-FU). Newly diagnosed early TNBC are treated by neoadjuvant chemotherapy, followed by surgery. In the case of relapsed/refractory TNBC, there is no standard chemotherapy regimen [39]. Responses to treatment are usually short in duration and followed by rapid relapse, and visceral and brain metastases are common. Available therapies for patients with advanced TNBC include anti-metabolites capecitabine and gemcitabine, non-taxane microtubule inhibitor eribulin, and DNA cross-linker platinums, such as carboplatin, oxaliplatin and cisplatin. Platinum salts function as DNA-damaging compounds that cause DNA strand breaks, resulting in apoptotic cell death; hence, they can be particularly effective in BRCA1/2 mutant TNBCs. Many studies have been investigating the effectiveness of platinum-based neoadjuvant chemotherapy in TNBC patients [40, 41]. To date, two immune checkpoint inhibitors (ICIs), pembrolizumab and atezolizumab, have been approved by the US Food and Drug Administration (FDA) and the EMA as first-line treatments, in association with chemotherapy for TNBC patients with PD-L1-positive metastatic disease on the basis of the results obtained from IMpassion130 [42] and KEYNOTE-355 [43] trials, respectively [44]. Atezolizumab is a humanized IgG1 moAb deriving from genetical engineering. It binds PD-L1, thus leading to the blockade of its interaction with PD-1. Monotherapy with atezolizumab was assessed in a phase I trial (NCT01375842), engaging 116 mTNBC patients under treatment with first- or second-line drugs [45]. Pembrolizumab is a humanized IgG4 kappa anti-PD-1 monoclonal antibody (moAb), which was first studied in the KEYNOTE-012 clinical trial (NCT01848834). After the results of KEYNOTE-522, it received approval from the FDA in July 2021 in association with chemotherapy as a neoadjuvant treatment and, after surgery, as a single agent for nine cycles of treatments of patients with high-risk stage II or III TNBC [46]. Immunotherapy and personalized therapies for TNBC and metastatic TNBC have been recently reviewed by Italian researchers [47, 48]. Post-neoadjuvant risk-adapted treatments have been shown to improve survival in TNBC patients with a high risk of recurrence [49]. Moreover, new strategies for the treatment of TNBC have been recently reported [50]. Sacituzumab govitecan (Trodelvy®) is a Trop-2-directed antibody and topoisomerase inhibitor drug conjugate, which recently received approval from the FDA and EMA for the treatment of mTNBC. In Italy, this drug is not used in clinical practice since it has not yet received approval by the Agenzia Italiana del Farmaco (AIFA, Rome, Italy) [51] even though new therapeutic targets are promptly needed to overcome the aggressiveness, strong metastatic potential, and low survival of these subtype of cancers [52].

2.3. Therapies for HER2-low Breast Cancers

In the last years, HER2-low BCs have been studied in depth by both oncologists and pathologists [53], and HER2-targeting antibody-drug conjugates are currently under study for this subtype of BC [54]. Phase I trials have revealed considerable clinical benefits in ABCs with HER2-low expression (HER2 IHC score = 1+ or 2+, without gene amplification) with the use of novel HER2-directed ADCs, such as trastuzumab-duocarmazine (SYD-985) and trastuzumab-deruxtecan (T-DXd, Enhertu®). Furthermore, the result of the phase III international clinical trial DESTINY-Breast-04 (D-B-04) published in June 2022 [55] demonstrated that T-DXd considerably enhanced the PFS (median 9.9 *vs* 5.1 months) and overall survival (OS, median 23.4 *vs* 16.8 months) in patients with HER2-low expressing metastatic BC receiving one or two previous lines of chemotherapy in comparison to physician's choice of chemotherapy, independently of HR status [56]. In August 2022, T-DXd received approval from the U.S. FDA as the first target therapy for patients with unresectable or metastatic HER2-low BC [57]. However, neutropenia was a common adverse effect in patients treated with T-DXd, occurring in about 70% of patients [55]. Moreover, interstitial lung disease/pneumonitis [58, 59] and cardiotoxicity [60] are well-described, serious, and show potentially life-threatening adverse events associated with T-DXd.

3. CLINICAL TRIALS FOR BREAST CANCERS

Several clinical trials that are ongoing worldwide are reported herein, focusing particularly on the studies carried out in Italy. However, it must be considered that the geographical distribution of clinical trials in Italy is generally heterogeneous [61]. The clinical studies carried out in Italy regarding different types of BC are depicted in Table **1**. The EUROPA trial (NCT04134598) is a phase 3 trial currently investigating the effects of breast irradiation and endocrine therapy with letrozole, anastrozole, exemestane and tamoxifen in BC [62]. A randomized, prospective, multicenter,

multi-basket, phase II clinical trial (NCT04591431) is aimed to evaluate the efficacy of tailored therapy *versus* standard of care in patients with metastatic solid tumors, including BC, who received at least one and no more than two lines of treatment [63]. However, the majority of studies are specifically related to the one type of BC, as summarized below.

3.1. Clinical Trials for Breast Cancers

3.1.1. Clinical Trials Specifically for HER2$^+$ Breast Cancers

Recent clinical trials ongoing for HER2$^+$ BC are reported in Table **2**. NeoSphere (NCT00545688) is a randomized, international, multicentre, open-label phase II study in women with LABC), inflammatory breast cancer (IBC) or HER2$^+$ early BC (EBC) [64, 65], which examines the safety and efficacy of the various combinations of the trastuzumab/pertuzumab, in the presence or absence of chemotherapy [66]. The study involves diverse countries in the world, including Italy (Dr. Gianni, L. at the Oncologia Medica, San Raffaele Cancer Centre, Milano; Morandi, P. at the Reparto di Oncologia Medica, Ospedale S Bortolo, Vicenza, Italy; Bianchi, G. at the Oncologia Medica 1, Fondazione IRCCS Istituto Nazionale Tumori, Milano, and Valagussa, P. at Fondazione Michelangelo, Milano). The study revealed a significantly higher pathologic complete response (pCR) rate for patients treated with neoadjuvant trastuzumab, pertuzumab, and docetaxel (Taxotere®, Sanofi-Aventis, Paris, France) (group B) compared to patients treated with trastuzumab + docetaxel (group A), pertuzumab + trastuzumab (group C), or pertuzumab + docetaxel (group D) (45.8% *versus* 29.0%, 16.8%, and 24.0%, respectively) [61]. CLEOPATRA (NCT00567190) is a phase III study evaluating pertuzumab + trastuzumab + docetaxel *versus* placebo + trastuzumab + docetaxel in previously untreated HER2$^+$ MBC. The final analysis from the CLEOPATRA study demonstrated an estimated median 15.7-month enhancement in OS when pertuzumab was used [67]. Recently, the end-of-study analysis of CLEOPATRA has been reported [68]: improvements in OS with trastuzumab, pertuzumab, and docetaxel *versus* placebo, trastuzumab, and docetaxel were retained after a median of more than 8 years of follow-up. The long-term and cardiac safety profiles of trastuzumab, pertuzumab, and docetaxel were retained in the overall population and in crossover patients. Thus, the association of trastuzumab, pertuzumab and docetaxel was established as standard first-line therapy for HER2$^+$ locally recurrent/metastatic breast cancer (LRBC/MBC). The global, open-label, multicentre single-arm phase II-Ib PERUSE (PERtUzumab global SafEty) study (NCT01572038) evaluated the safety and efficacy of pertuzumab and trastuzumab in combination with three extensively used taxanes in HER2$^+$ LRBC or MBC [69]. It was carried out in diverse countries, including Italy (Udine and Aviano) [70], and the results were consistent with the CLEOPATRA study, indicating that the median OS was higher than 5 years. Moreover, paclitaxel was suggested as a viable alternative to docetaxel. TRYPHAENA (NCT00976989) is a randomized, multicentre, open-label phase II study conducted in 44 centres present in 19 countries to assess the overall safety and cardiac toxicity of pertuzumab plus trastuzumab in association with anthracycline-containing and anthracycline-free regimens in neoadjuvant treatment of HER2$^+$ EBC [71]. The study carried out according to the guidelines for Good Clinical Practice and the Declaration of Helsinki, demonstrated high rates of pCR and good cardiac safety [72]. The APHINITY trial (NCT01358877) is a randomized, multicentre, double-blind, phase III placebo-controlled comparison of chemotherapy plus trastuzumab plus placebo or pertuzumab as adjuvant therapy for patients affected by operable HER2$^+$ primary BC. About 4,805 patients were engaged in 545 hospitals across 42 countries between November 2011 and August 2013 after they had given informed consent. The main aim was to compare invasive disease-free survival (IDFS; excluding second non-breast cancers) in patients with HER2$^+$ EBC randomized to chemotherapy + 1 year of trastuzumab + placebo or chemotherapy + 1 year of trastuzumab + pertuzumab. Eligible chemotherapy regimens comprised: 1) FEC (fluorouracil, epirubicin, cyclophosphamide) or FAC (fluorouracil, doxorubicin, cyclophosphamide), followed by docetaxel or paclitaxel; 2) anthracycline and cyclophosphamide (AC), followed by docetaxel or paclitaxel; 3) docetaxel in association with carboplatin. APHINITY, at 3-years and 45 months median follow-up, demonstrated that pertuzumab, in addition to adjuvant trastuzumab and chemotherapy, determined a significant improvement of IDFS for patients with HER2$^+$ EBC, particularly those with node-positive or HR-negative disease [72]. The second preplanned interim OS and descriptive updated IDFS analysis relative to 74 months median follow-up have been recently reported. Six-year OS was 95% *versus* 94%, with 125 deaths (5.2%) *versus* 147 (6.1%), respectively. IDFS analysis based on 508 events (intent-to-treat population) showed a hazard ratio of 0.76 (95% CI, 0.64 to 0.91) and 6-year IDFS of 91% and 88% for pertuzumab and placebo groups, respectively. Benefits in IDFS were seen in the node-positive but not in the node-negative cohort, and primary cardiac

events were found in less than 1%. This analysis confirms the IDFS benefits of adding pertuzumab to standard adjuvant therapy for patients with node-positive $HER2^+$ EBC; however, a longer follow-up is needed to fully assess OS benefits [73]. In a recent study belonging to APHINITY, carried out in different countries, including Italy (Prof. Viale, IEO European Institute of Oncology IRCCS, University of Milan), patients were divided into two arms: pertuzumab *versus* placebo arms. The study was addressed to investigate the health-related QoL (patient functioning/symptoms of therapy/global health status) and showed that improvement in invasive disease-free survival obtained by adding pertuzumab to trastuzumab and chemotherapy did not negatively influence the activities of daily living compared to trastuzumab and chemotherapy alone. Patient-reported diarrhea increased during taxane therapy in both arms and persisted during HER2-targeted treatment in the pertuzumab arm [74]. A recent study carried out also in Italy (Genoa, Prof. Lambertini) showed that pertuzumab and trastuzumab rise clinical outcomes, in comparison to trastuzumab alone, in $HER2^+$ EBC. The cardiac safety profile of the two drugs in patients enrolled in the APHINITY trial was investigated. After more than 6 years of median follow-up, trastuzumab and pertuzumab did not enhance cardiotoxicity risk compared to trastuzumab alone. Treatment with trastuzumab and pertuzumab determined a low incidence of cardiac events (about 3.5%), mostly reversible [75]. The randomized phase II PERTAIN trial (NCT01491737) examined the efficacy of trastuzumab plus an AI in the presence or absence of pertuzumab in order to evaluate the role of pertuzumab in $HER2^+$ and HR^+ metastatic or LABC. It was carried out in postmenopausal patients who were divided into two arms: pertuzumab plus trastuzumab plus AIs (anastrozole/letrozole) or trastuzumab + AIs. Benefits in PFS were observed in the three-drug arm [76]. An analysis from this study with more than 6 years of median follow-up provides additional evidence on the role of pertuzumab plus trastuzumab in the first-line treatment of HER2-positive MBC/LABC, suggesting some PFS benefits deriving from first-line trastuzumab/pertuzumab in combination with endocrine therapy; thus, chemotherapy-free treatment may be considered an interesting option in highly selected patients [77, 78]. The Phase 2 European Organization for Research and Treatment of Cancer (EORTC 75111-10114) is an open-label, randomized, phase II trial study regarding the use of pertuzumab and trastuzumab in the presence or absence of metronomic chemotherapy for older patients with $HER2^+$ MBC. It involves the group of Prof. Curigliano (Istituto Europeo di Oncologia, IRCCS, Italy and the University of Milan). The addition of metronomic oral cyclophosphamide to trastuzumab plus pertuzumab in frail and older patients enhanced median PFS (mPFS) by 7 months in comparison to dual HER2 blockade alone, with a suitable safety profile [79]. Recently, a therapy with T-DM1 after the metronomic chemotherapy-based dual blockade was evaluated in the EORTC 75111-10114 ETF/BCG study [80]. It was demonstrated to be an active and well-tolerated treatment alternative in an older/frail $HER2^+$ MBC population, with a median survival of more than 3 years in spite of the associated frailty in a major part of the studied population. T-DM1 provided a PFS rate at 6 months of 43.6% [81]. KRISTINE (NCT02131064) is a phase III trial of neoadjuvant T-DM1 + pertuzumab *versus* docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) in patients with $HER2^+$ BC, with a primary endpoint of pCR rate. KRISTINE showed that T-DM1 plus pertuzumab showed less toxicity, whereas docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) maintained an increased rate of pCR, not depending on hormone receptor status [82]. Recently, it has been reported that among 444 patients enrolled in the KRISTINE study, those with increased HER2 amplification/expression and levels of immune marker were associated with better responses irrespective of treatment arm [83]. The ATEMPT randomized clinical trial (NCT01853748) was carried out with Translational Breast Cancer Research Consortium (TBCRC)033 in patients with stage I $HER2^+$ BC who had undergone curative intent surgery, comparing the treatment with adjuvant T-DM1 and paclitaxel plus trastuzumab. One year of adjuvant T-DM1 was associated with excellent 3-year IDFS but not associated with fewer clinically relevant toxicity compared to paclitaxel + trastuzumab [84]. Recently, the ATEMPT trial (TBCRC033) has assessed that radiation therapy was well-tolerated when given contemporaneously to either T-DM1 or paclitaxel + trastuzumab [85]. The latter study, carried out also in Italy (Prof. Tarantino, European Institute of Oncology IRCCS, Milan), has demonstrated a low incidence of significant cardiac side effects during the therapy with adjuvant T-DM1 [86]. The phase 1b HER2-CLIMB study (NCT02614794) evaluated the combination of tucatinib with trastuzumab and capecitabine for patients with pretreated $HER2^+$ MBC in the presence or absence of brain metastases [87]. The combination with tucatinib was well tolerated, with a low rate of discontinuation because of side effects. For patients who did not receive fam-trastuzumab deruxtecan-nxki (T-DXd) in the second-line therapy, tucatinib represents a third-line treatment alternative based on results from the DESTINY-Breast01 phase II study [88]. The phase

Table 2. Clinical studies for HER2$^+$ breast cancers.

Name of the Study	Drugs	Phase Study	Outcomes
NeoSphere (NCT00545688)	Trastuzumab, docetaxel, pertuzumab	Phase II	Higher pCR rate for patients treated with pertuzumab, trastuzumab and docetaxel (45.8%) *versus* patients treated with trastuzumab plus docetaxel (29,0%), pertuzumab plus trastuzumab (16.8%), or pertuzumab plus docetaxel (24.0%).
CLEOPATRA (NCT00567190)	Pertuzumab, trastuzumab, docetaxel	Phase III	Estimated median 15.7-month improvement in OS when pertuzumab was used. Improvements in OS with pertuzumab, trastuzumab and docetaxel *versus* placebo, trastuzumab and docetaxel alone.
PERUSE (NCT01572038)	Pertuzumab, trastuzumab and taxanes	Phase IIIb	Higher median OS than 5 years. Paclitaxel was suggested as a viable alternative to docetaxel.
TRYPHAENA (NCT00976989)	Pertuzumab, trastuzumab and anthracycline	Phase II	High rates of pCR and evidence of cardiac safety with pertuzumab + trastuzumab in combination with both anthracycline-containing and anthracycline-free regimens.
APHINITY (NCT01358877)	Pertuzumab, trastuzumab and chemotherapy	Phase III	Improvement of IDFS, invasive disease-free survival and clinical outcomes if pertuzumab was added to trastuzumab and chemotherapy without increased cardiotoxicity risk compared to trastuzumab alone.
PERTAIN (NCT01491737)	Pertuzumab, trastuzumab and AIs	Phase II	Benefit in PFS when pertuzumab was added to trastuzumab + AIs (anastrozole/letrozole).
EORTC 75111-10114	Pertuzumab and trastuzumab with or without metronomic chemotherapy	Phase II	Enhanced mPFS by 7 months if metronomic oral cyclophosphamide was added to trastuzumab + pertuzumab in older and frail patients with an acceptable safety profile.
KRISTINE (NCT02131064)	T-DM1 + pertuzumab *versus* docetaxel + carboplatin + trastuzumab + pertuzumab (TCHP)	Phase III	Less toxicity with the association of T-DM1 + pertuzumab; docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) maintained a higher rate of pCR.
ATEMPT (NCT01853748) (TBCRC033)	Trastuzumab emtansine *versus* paclitaxel in combination with trastuzumab	Phase II	Adjuvant T-DM1 was associated with excellent 3-year IDFS and low incidence of significant cardiac adverse events.
HER2CLIMB (NCT02614794)	Tucatinib with capecitabine and trastuzumab	Phase 1b	Tucatinib combination was well tolerated, with a low rate of discontinuation because of adverse events.
MARGOT (NCT04425018)	Paclitaxel, margetuximab and pertuzumab *versus* paclitaxel, trastuzumab and pertuzumab	Phase II	Study results have not been submitted to clinicaltrials.gov. Estimated Primary Completion Date: 2024-07-01. Estimated Study Completion Date: 2027-07-01.
BERENICE (NCT02132949)	Pertuzumab, trastuzumab	Phase II	Cardiac safety of the neoadjuvant-adjuvant pertuzumab-trastuzumab-based therapy.

II MARGOT trial (NCT04425018) compares the treatment of the combination paclitaxel, margetuximab and pertuzumab and paclitaxel, trastuzumab and pertuzumab for 12 weeks before surgery in patients with anatomic stage II-III HER2$^+$ BC and who are CD16A F carriers. An additional phase II study (NC-

T04262804) evaluates the efficacy and safety of margetuximab + chemotherapy in $HER2^+$ MBC Chinese patients. Still ongoing is a phase I study (NCT01148849) assessing margetuximab in patients with refractory $HER2^+$ BC and in patients with other carcinomas that overexpress HER2 [89]. The results of this study have not been submitted to clinicaltrials.gov yet [90]. The phase II BERENICE clinical trial (NCT02132949) was conceived to incorporate pertuzumab in both neoadjuvant and adjuvant settings in order to complete 1 year of dual anti-HER2 therapy. It assessed the cardiac safety of the neoadjuvant-adjuvant pertuzumab-trastuzumab-based therapy for $HER2^+$ EBC patients at high risk [91]. A systematic literature review conducted by an Italian group of medical oncologists, an expert in BC treatment, studied the residual risk of relapse in a project that was aimed at defining the unmet needs of patients with $HER2^+$ non-metastatic BC, taking into consideration 6 studies: HERA, BCIRG 006, NSABP B-31, NCCTG N9831, APHINITY and KATHERINE. In conclusion, it was evidenced that, in spite of the available treatment alternatives, there is still a considerable medical need for some non-metastatic $HER2^+$ BC patients [92].

3.1.2. Clinical Trials Specifically for Triple Negative Breast Cancer

The randomized prospective WSG-ADAPT TN phase II trial (NCT01815242) compared the efficacy nab-paclitaxel + gemcitabine *versus* nab-paclitaxel + carboplatin, as a 12-week anthracycline-free chemotherapy regimen in TNBC [93]. Kolberg-Liedtke *et al.* [94] studied the effect of tumor-infiltrating lymphocytes (TILs) on the response of neoadjuvant chemotherapy in TNBC EBC. The study showed that immune processes marked by higher tumor-infiltrating lymphocyte measurements are associated with favorable response to neoadjuvant chemotherapy and a better survival rate. The multicentre, randomized, phase III trial, Ascent study (NCT02574455) engaged patients in North America and Europe in order to compare the therapy with sacituzumab govitecan and four single-agent types of chemotherapy, capecitabine, gemcitabine, vinorelbine, and eribulin, in mTNBC patients who were refractory or relapsed after at least two previous treatments with chemotherapy, including taxanes. A considerable prevalence of sacituzumab govitecan over chemotherapy was observed both in terms of survival and tolerable safety profile [95]. Other clinical studies regarding the use of VEGFR inhibitors are ongoing: ATRACTIB (NCT04408118) is a phase II trial of first-line atezolizumab in combination with paclitaxel and bevacizumab in mTNBC [96], whereas the NCT05192798 phase II trial investigates the first-line combination of bevacizumab and nab-paclitaxel [48].

3.1.3. Clinical Trials Specifically for HER2-low Breast Cancers

The treatment of HER2-low tumors in Europe has not been fully established yet [97]. Even though the new ADCs have shown improved clinical outcomes of HER2-low tumors, this innovating strategy is not yet available in clinical practice, and no anti-HER2 agents are now approved for HER2-low BCs treatment in Europe. In the NSABP B-47 trial, the addition of trastuzumab to adjuvant chemotherapy (CRx) did not improve IDFS, distant recurrence-free interval, or OS in patients with non-HER2-overexpressing invasive BC. Trastuzumab does not benefit women without an IHC score of 3+ or with fluorescence *in situ* hybridization ratio-amplified BC [98]. A recent study carried out primarily in Italy (Napoli, Potenza, Bari, Caserta, Parma) compared the outcomes of the treatment with endocrine therapy plus palbociclib as first-line therapy of patients with HR^+ MBCs, either in the presence of HER2-low or $HER2^-$ tumors. The same treatment showed similar survival outcomes in HR^+ MBC patients with HER2-low and $HER2^-$ tumors [99]. A second phase III trial, DESTINY-Breast06 (NCT04494425), is currently ongoing in order to assess the efficacy of T-DXd compared to the investigator's choice of chemotherapy in ER^+/HER2-low ABC resistant to endocrine therapy in the presence or absence of targeted treatments in patients who were not previously treated with chemotherapy [100, 101].

3.1.4. Clinical Studies Regarding Physical Activity and Breast Cancer

Physical activity plays a crucial role in several diseases, leading to positive effects in depression and anxiety [102], polycystic ovary syndrome [103], COVID-19 [104], and diabetes [105]. The usefulness of physical activity in BC has been widely recognized [106]. High recreational physical activity after BC diagnosis has been associated with lower all-cause and BC mortality [107]. In pre-and postmenopausal women, physical activity and exercise can cause a decrease in levels of select estrogens, progestogens, and androgens while stimulating a small increase in sex hormone binding globulin [108]. Notwithstanding the importance of physical activity in the management of BC, there are not many NCTs carried out in Italy regarding physical activity in BC. Thus, in the table below (Table **3**), we have reported the clinical studies carried out worldwide.

Table 3. Global clinical studies regarding physical activity in BC patients.

ClinicalTrials.gov Identifier (Location)	Title	Condition or Disease	Recruitment Status	Estimated Study Completion Date
NCT04354233 (France)	A Physical Activity Program to Improve Quality of Life and Reduce Fatigue in Metastatic Breast Cancer (ABLE02)	Metastatic Breast Cancer	Recruiting	June 2025
NCT03223753 (USA)	Web-Based Physical Activity Intervention in Improving Long-Term Health in Children and Adolescents with Cancer	Carcinoma *In situ* Hematopoietic and Lymphoid System Neoplasm Malignant Solid Neoplasm	Recruiting	March 31, 2025
NCT04024280 (Portugal)	Effects of a Physical Exercise Program on the Quality of Life of Breast Cancer Survivors (MamaMoveGaia)	Breast Cancer Quality of Life Physical Exercise	Completed	–
NCT04109274 (Canada)	Implementing Exercise into Clinical Practice in Breast Cancer Care (NEXT-BRCA)	Breast Cancer	Active, not recruiting	December 31, 2023
NCT04262180 (USA)	Physical Activity Promotion for Breast and Endometrial Cancer Survivors	Physical Activity Breast Cancer Survivors Endometrial Cancer Survivors	Active, not recruiting	March 21, 2024
NCT03548636 (Canada)	Project MOVE: Increasing Physical Activity Among Breast Cancer Survivors	Cancer Prevention	Completed	–
NCT04088708 (USA)	Gut Microbe Composition, Exercise, and Breast Breast Cancer Survivors (ROME)	Breast Cancer Gut Microbiome Exercise	Recruiting	August 31, 2025
NCT05704855 (Canada)	A Combined Exercise Training Program for Women Living with Breast Cancer	Breast Cancer	Recruiting	September 30, 2023
NCT04736576 (Pfizer, Japan)	Study to Evaluate Patient Reported Outcome (PRO) and Physical Activity in Japanese Patients with HR+/HER2- Advanced Breast Cancer Treated with Palbociclib Plus Endocrine Therapy or Endocrine Monotherapy (JBCRG-26)	Breast Cancer	Completed	–
NCT03564899 (Canada)	The Breast Cancer & Physical Activity Level (BC-PAL) Pilot Study (BC-PAL)	Breast Cancer Survivorship	Completed	–
NCT01795612 (France)	Adapted Physical Activity Effect on Aerobic Function and Fatigue at Home in Patients with Breast Cancer Treated in Adjuvant or Neoadjuvant Phase (APAC)	Breast Cancer	Completed	–
NCT01140282 (USA)	Exercise Program for Early Breast Cancer Survivors	Stage I Breast Cancer Stage II Breast Cancer Stage IIIA Breast Cancer Stage IIIB Breast Cancer Stage IIIC Breast Cancer	Completed	–
NCT02560662 (Sweden)	PhysSurg-B: Physical Activity in Relation to Surgical Operations - Breast Cancer (PhysSurg-B)	Breast Cancer	Completed	–
NCT04064892 (USA)	Physical Activity Intervention for Young Cancer Survivors	Breast Cancer Quality of Life Physical Activity	Completed	–
NCT03679559 (USA)	Exercise in Improving Health and Quality of Life in Breast Cancer Survivors	Invasive Breast Carcinoma	Completed	September 1, 2023
NCT03529383 (France)	Efficacy of Exercise Using Connected Activity Trackers and Therapeutic Education in Localized Breast Cancer (DISCO)	Breast Cancer	Completed	–
NCT01435005 (Canada)	Breast Cancer and Exercise Trial in Alberta (BETA)	Breast Neoplasms	Completed	–

(Table 3) contd….

ClinicalTrials.gov Identifier (Location)	Title	Condition or Disease	Recruitment Status	Estimated Study Completion Date
NCT03674515 (France)	Study of Program Interest "Bouge" to Improve the Daily Physical Activity in Processings Treatment of Non-metastatic Breast Cancer (BOUGE CANCER)	Physical Activity Breast Cancer Mobile Health Apps	Completed	–
NCT04298086 (USA)	A Study of the Body's Response to Exercise and a Plant-Based Diet in Overweight Postmenopausal Women with Breast Cancer	Breast Cancer Primary Hormone Receptor-Positive Breast Cancer	Active, not recruiting	March 2024
NCT04818359 (Urbino and Milan, Italy)	Movement and Health Beyond Care (MoviS) (MoviS)	Breast Cancer Survivors	Recruiting	November 30, 2025
NCT03314688 (USA)	Lifestyle, Exercise, and Nutrition Study Early After Diagnosis	Breast Neoplasms	Active, not recruiting	December 31, 2023
NCT06018051 (Turkey)	"Can Do" *versus* "Do Do" in Patients with Breast Cancer	Breast Cancer Exercise Capacity Physical Activity	Not yet recruiting	July 1, 2024
NCT06002022 (Spain)	Local Intervention Trial for the Evaluation of Improvements in Patient-reported Quality of Life and Treatment Satisfaction in Breast Cancer Patients (BCP), as a result of Flexible Treatment Planning Supported by REBECCA-collected Real-world Data (REBECCA-QoL)	Breast Cancer Quality of Life Physical Activity Sleep Quality Stress Pain	Not yet recruiting	December 31, 2025

4. QUALITY OF LIFE STUDIES REGARDING BREAST CANCER PATIENTS

RCT studies do not always give results that truly mirror real life. Thus, there are some studies that are specifically addressed to RL. A retrospective study [109] on 155 patients treated outside clinical trials was conducted in 8 Italian Institutes (the University of Naples Federico II (Naples); Cardarelli Hospital (Naples); National Cancer Institute G. Pascale (Naples); National Cancer Institute - Regina Elena (Rome); San Carlo Hospital (Potenza); Hospital Vito Fazi (Lecce); University Hospital of Udine (Udine); and Santa Chiara Hospital of Pisa (Pisa)) to evaluate the efficacy and safety profile of pertuzumab in RL patients, comparing it to CLEOPATRA trial. The efficacy of anti-HER2 treatment with pertuzumab in combination with trastuzumab and a taxane as the first-line treatment for HER2-positive MBC was evaluated. The study carried out in Italy confirmed the value of first-line treatment with taxanes + trastuzumab and pertuzumab in $HER2^+$ metastatic BC. Exposure to taxanes was comparable in CLEOPATRA and RL patients. The median number of taxane cycles was 8 (range: 1-42) in CLEOPATRA patients and 7 (1-14) and 6 (1-15) for docetaxel and paclitaxel, respectively, in RL patients.

Moreover, mPFS was unexpectedly much higher in the RL setting than in the CLEOPATRA trial (27.8 *vs* 18.5 months, respectively). mPFS of the study by De Placido *et al.* [109] was also better than that of the phase II VELVET study (27.8 *vs* 14.3 months), even though in the latter trial, pertuzumab and trastuzumab were administered in combination with vinorelbine. QoL is one of the most debated issues for oncology patients because of its multidimensional features and is perceived as something that affects the patients' lifestyle starting from the first diagnosis. The continuous advancements in prevention, early detection and therapies allowed to prolong the expected survival time of patients. As a direct consequence, the interest in assessing the health-related QoL of survivors and realizing the necessary interventions that can improve cancer-related issues from a psychological and physical point of view has notably increased [110]. Several studies are being carried out on patient-reported outcomes and their use in clinical practice and clinical trials. The European Organization for Research and Treatment of Cancer (EORTC) Breast Module is a disease-specific questionnaire designed in order to assess QoL in patients with BC. One of the first modules, EORTC QLQ-BR23, was developed in 1996, consisted of 23 items, and was translated into more than 60 languages [111]. It was then used in conjunction with the core questionnaire, the EORTC QLQ-C30 and the results from these studies indicated an urgent need for psychosocial support prior to treatment [112]. In the last years, the EORTC QLG has introduced a four-phase methodology (EORTC QLQ-BR45) for developing modules: phase I consists of the generation of a list of QoL issues relevant to the selected group of patients; phase II transforms the issues into a provisional questionnaire; Phase III involves the questionnaire pre-

test, for acceptability and relevance, and for preliminary psychometric properties. Finally, phase IV has been designed to evaluate/confirm the psychometric properties of the questionnaire in an international field study. The final phase IV study is underway to confirm the psychometric properties of the module. The final version of the EORTC QLQ-BR45 is now available for use in clinical practice and is translated into 19 different languages [113]. In this study, the Unit for Psycho-oncology, Veneto Institute of Oncology IOV - IRCCS, Padua and the National Tumor Institute, Instituto Nazionale Tumori Fondazione Pascale Naples, both in Italy (Serpentini and Pinto, respectively), were involved. An interesting study was recently carried out in Italy to evaluate the association between positive personal resources (*i.e.*, optimism, hope, trait mindfulness, courage, and self-efficacy), resilience, and psychosocial distress (*i.e.*, anxiety, depression, stress) in BC patients and survivors during the pandemic of COVID-19 [114]. The authors found that personal positive resources had a straightforward positive effect on resilience, thus preventing distress. These findings were not affected by the level of exposure to COVID-19 [115]. Moreover, numerous studies have shown that physical activity represents an effective intervention to enhance QoL in cancer survivors and reduce fatigue, anxiety, and depression [116-118]. The "Operation Phalco", which is an experimental training protocol carried out in Italy for BC survivors enforced through oncologists, sports medicine physicians and kinesiologists network, evidenced the positive impact of a well-adapted physical activity on BC patients' QoL [119].

CONCLUSION

BC is one of the most frequent cancers among women worldwide. Novel therapies for BC are constantly emerging, such as targeted therapy and immunotherapy. However, there are still many women who die from this disease. Several research groups in Italy have focused their attention on cutting-edge studies regarding BC. Results from the three subtypes of BC considered in the study are diverse. The treatment of early and advanced $HER2^+$ MBC patients has advanced since the use of the first generation of "passive immunotherapy" based on HER2-directed monoclonal antibodies. However, it is also true that the combined use of immune checkpoint inhibitors resulted in controversial and, in some cases, disappointing outcomes. The main reasons include the low anti-tumor effects and the very different response between early and metastatic cancers. Thus, it is quite evident that the adoption of immunotherapy in the early setting for patients with $HER2^+$ MBC may represent a more promising strategy. However, additional efforts must be made to identify the predictive biomarkers for a more appropriate selection of patients who can benefit from immunotherapy. Finally, the study and management of long-term immune-related side effects should also be performed with particular attention. Different drugs produced positive clinical evidence for HER2-low MBC treatment, provided that HER2 expression levels have been detected with maximal accuracy. For instance, ADC analogs produced undoubted efficacy, with some exceptions in early-stage tumors that are still managed as HER2-negative tumors and treated as ER+/ER- tumors. On the contrary, the first-line treatment with T-DXd is very promising against the advanced stage HER2-low MBC, eventually supported with immunotherapy, chemotherapy or endocrine therapy. As well in this case, the most important obstacle to be overcome in the future is the low number of studies, whose increase may provide the empirical bases and new chances for a tailored HER2-low MBC therapy. Neutropenia, interstitial lung disease/pneumonitis, and cardiotoxicity are the most significant toxicities associated with T-DXd. Some recent results on TNBC treatment have been reached, mostly for PD-L1 positive tumors treated with ICIs, but the resistance development and relapse still represent the major problems that can compromise the survival endpoints. The real-time monitoring of these cancers and the therapy modulation may succeed in providing important clinical benefits as event-free and OS. However, disparities in the distribution of risk factors and in accessing early diagnosis and effective treatments still exist, mostly because of social, economic, and geographic differences in Italy. The implementation of screening programs for early detection of BC onset, which is strictly related to better therapeutic outcomes, survival, and QoL, is the major and desirable goal to reach.

Moreover, physical activity can positively influence the success of the therapy. From this perspective, further clinical studies in Italy would be desirable. This review represents useful literature to guide oncologists to treat patients and medicinal chemists to design and develop new synthetic strategies for the treatment of BC patients, overcoming adverse effects, resistance, and all other aspects of toxicity related to therapies currently used.

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The study concept was given by D.I. and A.C.; the original draft was prepared by J.C. and A.C.; writing, reviewing, and editing were assisted by A.M., D.B.,

C.S. and M.S.S.; data curation was done by D.I., C.R. and F.G.; supervision was provided by P.L. and M.S.S. All authors read and agreed to the published version of the manuscript.

LIST OF ABBREVIATIONS

ABC	=	Advanced Breast Cancer
ADCs	=	Antibody-drug Conjugates
AIFA	=	Agenzia Italiana Del Farmaco
AIs	=	Aromatase Inhibitors
BC	=	Breast Cancer
EBC	=	Early Breast Cancer
EMA	=	European Medicines Agency
EORTC	=	European Organization for Research and Treatment of Cancer
ER	=	Estrogen Receptor
HER2	=	Human Epidermal Growth Factor 2 Receptor
FDA	=	Food and Drug Administration
HR	=	Hormone Receptor
IBC	=	Inflammatory Breast Cancer
IDFS	=	Invasive Disease-free Survival
IHC	=	Immunohistochemical
LABC	=	Locally Advanced Breast Cancer
LRBC	=	Locally Recurrent Breast Cancer
MBC	=	Metastatic Breast Cancer
mPFS	=	Median Progression-free Survival
OS	=	Overall Survival
pCR	=	Pathologic Complete Response
PFS	=	Progression-free Survival
PR	=	Progesterone Receptor
QoL	=	Quality of Life
SERDs	=	Selective ER Degraders
SERMs	=	Selective ER Modulators
T-DM1	=	Trastuzumab Emtansine
T-DXd	=	Trastuzumab Deruxtecan
TNBC	=	Triple-negative Breast Cancer

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