Seminars in Oncology 47 (2020) 278–292

Contents lists available at ScienceDirect

Seminars in Oncology

journal homepage: www.elsevier.com/locate/seminoncol

Landmark trials in the medical oncology management of early stage breast cancer

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ARTICLE INFO

Article history:
Received 29 July 2020
Accepted 3 August 2020

Key words:
Breast cancer
Clinical trials
Hormone receptor
HER-2
Triple negative
Adjuvant
Neoadjuvant trastuzumab
Pertuzumab
T-DM1
Trastuzumab emtansine

ABSTRACT

With the advent of breast cancer screening programs, the majorities of patients with newly diagnosed breast cancer are diagnosed with early stage disease and are likely to experience cure with proper treatment. Significant advances have been made in the management of early-stage breast cancer to personalize treatment according to disease biology. This progress has led to improvement in survival outcomes and quality of life for our patients. In this review, we discuss landmark clinical trials in medical oncology that have shaped the current standard of care for early stage ER-positive, HER2-positive, and triple negative breast cancer.

Introduction

Breast cancer is the most commonly diagnosed cancer in women worldwide and the second leading cause of cancer-related deaths among women in the United States. There will be an estimated 276,000 new cases of breast cancer and 63,000 deaths due to breast cancer in the United States in 2020 [1]. Fortunately, the majorities of patients with newly diagnosed breast cancer have early stage disease and thus have a high chance of cure [2]. Early

Abbreviations: **ABC**, Anthracyclines in Early Breast Cancer; **AC**, adriamycin + cyclophosphamide; **ACTH**, adriamycin + cyclophosphamide + paclitaxel + trastuzumab; **AI**, aromatase inhibitor; **AJCC**, American Joint Committee on Cancer; **ALTERNATE**, Alternate approaches for clinical stage II-II estrogen receptor positive breast cancer neoadjuvant treatment; **ASCO**, American Society of Clinical Oncology; **ATLAS**, Adjuvant Tamoxifen, Longer Against Shorter; **aTTOM**, Adjuvant Tamoxifen - To Offer More?; **BRCA**, **br**east **ca**ncer gene; **BWEL**, The Breast Cancer Weight Loss; **CI**, confidence interval; **CALGB**, Cancer and Leukemia Group B; **CLBC**, contralateral breast cancers; **CMF**, cyclophosphamide + methotrexate + 5-fluorouracil; **CREATE-X**, Capecitabine for Residual Cancer as Adjuvant Therapy; **CDK**, cyclin-dependent kinase; **ddAC-T**, dose-dense doxorubicin and cyclophosphamide followed by paclitaxel; **DDFS**, distant disease-free survival; **DFS**, disease-free survival; **EBCTCG**, Early Breast Cancer Trialists Collaborative Group; **EFS**, event free survival; **EGFR**, epidermal growth factor receptor; **ENERGY**, Exercise and Nutrition to Enhance Recovery and Good Health for You; **ER**, estrogen receptor; **ET**, endocrine therapy; **HER2**, human epidermal growth factor receptor 2; **HORG**, Hellenic Oncology Research Group; **HP**, trastuzumab + pertuzumab; **HR**, hazard ratio; **HR negative**, hormone receptor negative; **HR positive**, hormone receptor positive; **IBCSG**, International Breast Study Group; **IDFS**, invasive disease-free survival; **ITT**, intention-to-treat; **LISA**, Lifestyle Intervention in Adjuvant Treatment of Early Breast Cancer; **LN**, lymph node; **LVEF**, left ventricular ejection fraction; **LVSD**, left ventricular systolic dysfunction; **MINDACT**, Genetic Testing or Clinical Assessment in Determining the Need for Chemotherapy in Women With Breast Cancer That Involves No More Than 3 Lymph Nodes; **NACT**, neoadjuvant chemotherapy; **NATALEE**, New Adjuvant Trial with LEE; **NCCTG**, North Central Cancer Treatment Group; **NET**, neoadjuvant endocrine therapy; **OFS**, Ovarian Function Suppression; **OS**, overall survival; **NCCN**, National Comprehensive Cancer Network; **NSABP**, National Surgical Adjuvant Breast and Bowel Project; **PALLAS**, Palbociclib Collaborative Adjuvant Study; **pCR**, pathologic complete response; **PFS**, progression-free survival; **PlanB**, West German Study Group PlanB; **PR**, progesterone receptor; **RFS**, relapse-fee survival; **RR**, relative risk; **RS**, 21-gene recurrence score; **RxPONDER**, Treatment for Positive Node, Endocrine Responsive Breast Cancer; **SERM**, selective estrogen receptor modulator; **TAILORx**, The Trial Assigning Individualized Options for Treatment; **TC**, docetaxel + cyclophosphamide; **TCH**, docetaxel + carboplatin + trastuzumab; **T-DM1**, trastuzumab emtansine, KADCYLA®; **TH**, paclitaxel + trastuzumab; **THP**, docetaxel + trastuzumab + pertuzumab; **TNBC**, triple-negative breast cancer; **WHEL**, Women's Healthy Eating and Living; **WINS**, Women's Intervention Nutrition Study.

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https://doi.org/10.1053/j.seminoncol.2020.08.001
0093-7754/

stage breast cancer consists of stage I-III disease as determined by the 8 edition of the American Joint Committee on Cancer staging manual and clinical subtype is determined by estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) status [3]. A multidisciplinary approach to early stage breast cancer typically involving surgical, radiation, and medical oncology is a standard of care and associated with optimal outcomes [4]. Treatment approach depends on extent of disease and clinical subtype. Significant advances in breast cancer research over the past 5 decades have resulted not only in improvement in survival, but also enhanced patients' quality of life [5]. Here we review the landmark trials in early-stage breast cancer which have established the current standard of care in medical oncology.

Principles of chemotherapy for early stage breast cancer

Adjuvant chemotherapy

Adjuvant chemotherapy after primary breast surgery has demonstrated improvement in survival outcomes, and through decades has morphed into current standard regimens [6]. In the mid 1970s, the first adjuvant polychemotherapy consisted of cyclophosphamide plus methotrexate and fluorouracil [7]. In the 1990s, use of anthracycline-based chemotherapy regimens were found to be superior to non-anthracycline containing regimens with better tolerance [8–12]. In an Early Breast Cancer Trialists Collaborative Group (EBCTCG) meta-analysis, use of anthracycline-containing regimens compared with no treatment resulted in 8% reduction in 10-year risk of breast cancer recurrence (39.4 *v* 47.4%, RR 0.73, 95% CI 0.68–0.79), 6.5% reduction in breast cancer mortality (29.3% *v* 35.8%, RR 0.79, 95% CI 0.72–0.85), and 5% reduction in overall mortality (34.6 *v* 39.6%, RR 0.84, 95% CI 0.78–0.91) [13]. Additionally, the addition of a taxane to an anthracycline-based chemotherapy regimen further reduced breast cancer mortality by 4.6% (30.2 *v* 34.8%, RR 0.86, 95% 0.79–0.93). Benefits of taxane incorporation were independent of age, nodal status, tumor size, tumor grade, and ER status [13].

Increased dose-intensity and sequential administration of anthracycline and taxane chemotherapy were found to reduce the risk of recurrence and death from breast cancer without increasing mortality from other causes, particularly in women with hormone receptor negative (HR-negative) breast cancer [14,15]. Compared to standard schedule chemotherapy, dose-intense administration (otherwise known as dose-dense) reduced 10-year risk of breast cancer recurrence by 3.4% (28.0 *v* 31.4%, relative risk [RR] 0.86, 95% confidence interval [CI] 0.82–0.89), breast cancer mortality by 2.4% (18.9 *v* 21.3%, RR 0.87, 95% CI 0.783–0.92), and all-cause mortality by 5.9% (22.1 *v* 24.8%, RR 0.87, 95% CI 0.83–0.91). Sequential anthracycline plus taxane chemotherapy was associated with reduction in 10-year risk of disease recurrence by 3.2% (28.1 *v* 31.3%, RR 0.87, 95% CI 0.80–0.94) [14]. While the improvement in disease recurrence rates with dose-intense chemotherapy were significant in both ER-positive and ER-negative disease, subsequent studies show that the likely benefit is in luminal B-like (PR $<$20% and/or Ki67 $\geq$20%) breast cancers compared to luminal A-like (PR $\geq$20% and Ki67 $<$20%) breast cancers [16–19].

An anthracycline is often used for HER2-negative, lymph node (LN) positive or high-risk LN-negative breast cancer. The Anthracyclines in Early Breast Cancer trials were a series of adjuvant trials that compared taxane-based regimens to anthracycline-taxane-based regimens. The primary endpoint of the analysis ($n = 4{,}242$) was to determine if a non-anthracycline based regimen was noninferior to an anthracycline-based regimen with respect to invasive disease-free survival (IDFS) [20]. While the trials failed to demonstrate noninferiority (4-year IDFS 88.2% *v* 90.7%, HR 1.23, 95% CI 1.01–1.50), planned exploratory analyses suggested that the magnitude of benefit for anthracycline-taxane-based regimens was greatest among patients with HR-negative tumors irrespective of nodal status, and those who are both hormone receptor positive (HR-positive) with LN-positive disease [20].

In summary, these data demonstrate that anthracycline and taxane based chemotherapy are the standard of care for early stage breast cancer. However, in patients with HR-positive, HER2-negative, LN-negative disease for whom chemotherapy is recommended, a taxane-based regimen such as docetaxel plus cyclophosphamide (TC) is preferred given the shorter duration of treatment and the lack of cardiac toxicity and secondary acute leukemia associated with anthracyclines [20,21]. In patients with a significant LN burden, an anthracycline-taxane-based regimen such as dose-dense doxorubicin and cyclophosphamide followed by paclitaxel (ddAC-T) administered weekly or in a dose-dense fashion ddAC-T should be considered if there are no contraindications. In patients with HR-positive, HER2-negative disease and low volume LN burden (0-3 LN-positive), either ddAC-T or TC may be considered based on patient preference, comorbidities, and the expected benefit from chemotherapy [6]. Furthermore, the advent of anti-HER2 therapy resulted in different systemic strategies for HER2-positive disease.

Role of neoadjuvant therapy

No significant difference in long-term outcomes has been reported with neoadjuvant *v* adjuvant systemic chemotherapy [22,23]. In an EBCTCG meta-analysis, no difference was seen in distant recurrence rate (38.2% *v* 38%, RR 1.02, 0.92–1.14) or breast cancer mortality (34.4% *v* 33.7%, RR 1.06, 0.95–1.18) in patients treated with neoadjuvant chemotherapy (NACT) compared to adjuvant chemotherapy at 15-year follow-up. [24]. Historically, the primary indication of pre-operative systemic therapy has been to improve surgical outcomes by rendering inoperable tumors resectable, down-staging patients with operable cancers desiring breast conservation, and more recently de-escalation of axillary surgery in those with clinically positive nodes [25,26].

Response to neoadjuvant therapy also provides important prognostic information and may inform adjuvant therapy recommendations for patients with triple-negative breast cancer (TNBC) and HER2-positive disease. Achieving a pathologic complete response (pCR) to neoadjuvant therapy has been associated with favorable outcomes in patients with TNBC and HER2-positive breast cancer [27–29]. In a pooled analysis of nearly 12,000 patients who received NACT, pCR was associated with significant improvement in event free survival (EFS) for patients with TNBC (hazard ratio [HR] 0.24, 95% CI 0.18–0.33) and patients with HER2-positive, HR-negative disease who received trastuzumab (HR 0.15, 95% CI 0.09–0.27) [28]. Based on findings from the Capecitabine for Residual Cancer as Adjuvant Therapy (CREATE-X) and KATHERINE randomized trials, patients with TNBC who do not achieve pCR following NACT may benefit from adjuvant capecitabine and patients with HER2-positive breast cancer who do not achieve pCR following NACT benefit from adjuvant trastuzumab emtansine (T-DM1, KADCYLA), respectively [30,31].

Management of HR-positive early stage breast cancer

Role for adjuvant chemotherapy

With few exceptions, all patients with HR-positive breast cancers should be considered candidates for adjuvant endocrine therapy (ET). The decision to proceed with adjuvant chemotherapy depends on the predicted risk of disease recurrence and estimated benefit from chemotherapy. Validated risk calculators have been

developed to estimate a specific patient's risk of breast cancer recurrence and mortality (eg, PREDICT) [32]. These include tumor factors such as LN status, grade, size, and patient factors such as age and menopausal status. However, these calculators do not consider the individual biologic characteristics of the patient's tumor and may lead to over- or under-treatment. Thus, genomic assays were developed to provide additional prognostic information and predict benefit from chemotherapy.

There are various gene expression assays to provide prognostic and therapy-predictive information that complements staging and biomarker information (Table 1), and the 21-gene assay is preferred by the National Comprehensive Cancer Network Breast Cancer Panel for node-negative breast cancer [6]. Other assays can provide additional prognostic information in patients with 1-3 positive LNs but are unknown if predictive of chemotherapy benefit in 1-2 positive LNs.

If a patient is a candidate for chemotherapy, current guidelines recommend obtaining a 21-gene Recurrence Score (RS) for patients with HR-positive, HER2-negative, LN-negative breast cancer with tumors >0.5-cm [6]. In all patients with high RS (RS >25 or RS ≥31) chemotherapy should be considered [33]. The Trial Assigning Individualized Options for Treatment (TAILORx) study was designed to determine if the addition of chemotherapy to ET provided any benefit for patients with HR-positive, HER2-negative, and LN-negative tumors with mid-range RS (RS 11–25) who otherwise met criteria for adjuvant chemotherapy based on tumor characteristics. There was no difference in outcomes between the 2 groups and 9-year overall survival (OS) was approximately 94% for the intention to treat population. In an exploratory analysis, some chemotherapy benefit was shown for women age <50 years with RS 16–25 [34]. Thus, current guidelines recommend ET alone for patients with a low RS score (RS<25) [6]. As some chemotherapy benefit was shown for women age <50 years with RS 16–25, chemotherapy may be considered for these patients [34].

The prognostic value of the RS has also been evaluated for patients with HR-positive, HER2-negative, LN-positive breast cancers [35–37]. Secondary analysis of a prospective registry of women with HR-positive, LN-positive tumors demonstrated a 5-year risk of recurrence of 2.7% in patients with an RS <18 treated with endocrine monotherapy [38]. In the West German Study Group PlanB (PlanB) study, women with HR-positive and LN-negative tumors and an RS <11 had a 5-year disease-free survival (DFS) of 94.4% with endocrine monotherapy [36]. Patients with HR-positive, 1-3 LN-positive and RS ≥18 should be considered for adjuvant chemotherapy due to increased risk of recurrence. However, the optimal RS cut-off to predict chemotherapy benefit in LN-positive disease remains unknown. The randomized phase 3 Treatment for Positive Node, Endocrine Responsive Breast Cancer trial is currently ongoing (NCT01272037) and aims to answer this question [39].

The 70-gene signature test is prognostic and classifies tumors as high or low genomic risk based on risk of recurrence at 5-year and 10-year. In the MINDACT study, this 70-gene signature predicted benefit from adjuvant chemotherapy in patients with LN-negative or 1-3 LN-positive disease who were deemed high clinical risk according to anatomical and pathologic characteristics. Women with discordant clinical and genomic risk results were randomized to chemotherapy versus no chemotherapy. After 5 years of follow-up, among patients with high clinical risk and low genomic risk breast cancers there was no significant difference with respect to distant disease-free survival (DDFS) and OS with chemotherapy versus no chemotherapy (5-year DDFS 93.3% *v* 90.3%; 5-year OS 98.8% *v* 97.3%) [40]. In updated analysis presented at American Society of Clinical Oncology 2020, 8-year DDFS and OS were not significantly different with chemotherapy versus no chemotherapy [41]. However, of these women with high clinical risk and low genomic risk, a small percentage still benefited from chemotherapy.

Adjuvant ET

Tamoxifen

Adjuvant ET significantly improves outcomes for patients with early stage HR-positive breast cancer. Tamoxifen is a selective estrogen receptor modulator and was historically the standard adjuvant treatment for all patients with HR-positive breast cancers until the introduction of aromatase inhibitors (AI), which were developed for postmenopausal women and are also currently used in premenopausal women receiving ovarian suppression. Tamoxifen remains among the primary adjuvant ET options for premenopausal women and a secondary option for postmenopausal women who are intolerant of an AI. EBCTCG analyses have demonstrated that 5-year of adjuvant tamoxifen reduces local, contralateral, and distant breast cancer recurrence by 30%–50% for the first 10-year after diagnosis. In addition, breast cancer mortality is reduced by about one-third for the first 15 years after diagnosis irrespective of tumor features, use of adjuvant chemotherapy and age [42,43].

While 5-year of adjuvant tamoxifen is the historical standard, studies show benefit to extending therapy to 10-year. In the Adjuvant Tamoxifen, Longer Against Shorter trial, patients treated with tamoxifen for 10 years had a reduction in the cumulative risk of breast cancer recurrence by 3.7% and breast cancer mortality by 2.8%, in years 5–14 of follow-up compared to those treated for 5 years [44]. Similarly, in the Adjuvant Tamoxifen–To Offer More? study, 10 years of tamoxifen was associated with 2.6% reduction in breast cancer recurrence, which was most notable beyond year 7 and 1.4% reduction in breast cancer mortality [45,46]. In both studies, there was a small increased risk of endometrial cancer and thromboembolic events. However, meta-analysis shows that endometrial cancer risk with tamoxifen is correlated with age; there was little absolute risk for patients younger than 54, but for entry age 55–69 years the 15-year incidence of endometrial cancer was 2.6% greater for the tamoxifen groups compared to the control group (3.8% *v* 1.1%, 95% CI 1.4–3.8) [43]. These studies are summarized in Table 1.

AI

AIs are preferred over tamoxifen for most postmenopausal women with HR-positive breast cancer. A meta-analysis from the EBCTCG of postmenopausal women with ER-positive breast cancer compared AIs to tamoxifen in 3 cohorts: (1) 5-year of AI versus 5-year of tamoxifen, (2) Tamoxifen alone versus short course of tamoxifen followed by AI for 5-year total of ET, and (3) AI alone versus short course of tamoxifen followed by AI for 5 total years of ET. Treatment with AI in each cohort resulted in reduced risk of breast cancer recurrence during the treatment period compared with tamoxifen with no further impact beyond the 5-year treatment period, and 20% reduction in breast cancer mortality [47]. Evidence suggests comparable outcomes and tolerability between different AIs thus all are appropriate options for those warranting treatment.

In the MA.17 study, 5-year of letrozole after completion of 5-year of tamoxifen was associated with improved DFS and OS compared to placebo [48]. Likewise, in the National Surgical Adjuvant Breast and Bowel Project (NSABP) B33 trial which included only patients with LN-positive breast cancer, 5-year of exemestane following 5-year of tamoxifen improved relapse-free survival [49]. These studies support sequential strategy for extended ET incorporating tamoxifen for 2–3 years or 5 years followed by AI for up to 5 years.

Studies evaluating the role of extended AI beyond 5-year have yielded mixed results. Both the MA.17R and NSABP B42 trial reported improvement in DFS and reduction in contralateral breast cancer [50–52]. Conversely, both the DATA and IDEAL trials failed

Table 1
Landmark trials in HR-positive breast cancer.

Study	Number	Population	Study design	Outcomes
Gene expression assays for consideration of adjuvant chemotherapy				
NSABP B20 [33]	N = 651	• LN-negative	• Tamoxifen versus Tamoxifen plus chemotherapy	• RS <11: 10-year DDFS: 98% versus 95% • RS 11–25: 10-year DDFS: 95% versus 94% • RS >25: 10-year DDFS: 63% versus 88%, HR 0.285 (0.15–0.55); P <.0001
TAILORx [34]	N = 6,711	• HER2-negative • LN-negative • Tumors >1-cm (or >0.5-cm with unfavorable histology)	• ET versus ET plus chemotherapy	• RS 11–25 • 9-year DFS: 83% versus 84% Age ≤50, RS 16–20: HR 1.9 (1.27–2.84); P = .0016Age ≤50, RS 21–25: HR 1.7 (1.03–2.90); P = .035 • 9-year DDFS: 94.5% versus 95% • 9-year OS: 94% versus 94%
MINDACT [40,41]	N = 1,550	• Majority HR(+) and HER2(-) • LN-negative or 1–3 LN-positive (48%)	• Chemotherapy versus no chemotherapy	High clinical risk and low genomic risk: • 5-year DDFS: 94% versus 96% • 5-year DFS: 90% versus 93%, HR 0.64 (0.43–0.95); P = .03 • 5-year OS: 97% versus 98%
Adjuvant endocrine therapy				
aTTom, [45,46]	N = 6,953	• 40% ER-positive (60% ER-unknown) • 31% LN-positive • Completed 5 years of adjuvant tamoxifen	• Continue tamoxifen for additional 5 years (10 years) versus stop tamoxifen (5 years)	• Recurrence rate: 17% versus 19%; P = .003 Years 7–9: RR 0.84 (0.73–0.95)Years ≥10: RR 0.75 (0.66–0.86) • Breast cancer mortality: 392 versus 443 deaths; P = .05 Years ≥10: RR 0.77 (0.64–0.92) • Overall mortality: 849 versus 910 deaths; P = .1 Years ≥10: RR 0.86 (0.75–0.97)
ATLAS [44]	N = 6,846	• 90% postmenopausal • 46% LN-positive • Completed 5 years of adjuvant tamoxifen	• Continue tamoxifen for additional 5 years (10 years) versus stop tamoxifen (5 years)	• Risk of recurrence: 21% versus 25%; P = .002 Years ≥10: RR 0.75 (0.62–0.90) • Breast cancer mortality: 12% versus 15%; P = .01 Years ≥10 years: RR 0.71 (0.58–0.88) • Overall mortality: 639 versus 722 deaths; P = .01 All years: RR 0.87 (0.78–0.97)
MA.17 [48]	N = 5,187	• Postmenopausal • 45% LN-positive • Completed 5 years of adjuvant tamoxifen	• Letrozole for additional 5 years versus placebo • Allowed for cross-over	• 4-year DFS: 94% versus 91%, HR 0.68 (0.55–0.83); P <.001 LN-negative: HR 0.51 (0.35–0.75); P = .0005 LN±: HR 0.74 (0.58–0.94); P = .01 • Annual rate of CLBC: 0.3% versus 0.5%, HR 0.61 (0.39–0.97); P = .003 • No significant difference in DDFS or OS
NASBP B33 [49]	N = 1,598	• Postmenopausal • 100% LN-positive • Completed 5 years of adjuvant tamoxifen	• Exemestane for additional 5 years versus placebo • Allowed for cross-over	• 4-year DFS: 91% versus 89%; RR 0.68; P = .07 • 4-year RFS: 96% versus 94%; RR 0.44; P = .004 • 4-year incidence of CLBC: 2 versus 8 events; P = .05 • No significant difference in DDFS or OS

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Table 1 (*continued*)

Study	Number	Population	Study design	Outcomes
MA.17R [52]	N = 1,918	• Postmenopausal • 53% LN-positive • Completed 5 years of AI and/or tamoxifen	• Letrozole for additional 5 years versus placebo	• 5-year DFS: 95% versus 91%, HR 0.66 (0.48–0.91); $P = .01$ • 5-year OS: 93% versus 94% • Annual rate CLBC: 0.21% versus 0.49%; HR 0.42 (0.22–0.81); $P = .007$
NSABP B42 [49–51]	N = 3,923	• Postmenopausal • 57% LN-positive • Completed 5 years of AI and/or tamoxifen	• Letrozole for additional 5 years versus placebo	• 10-year DFS: 76% versus 72%; HR=0.84 (0.74–0.96); $P = .01$ T≤2 tumors: HR 0.63 (0.49–0.82) T≧2 tumors: HR 0.93 (0.80–1.09) (interaction $P = .013$) • 10-year OS: 86% versus 85.5% • 10-year BCFI: HR 0.74 (0.61–0.91); $P = .003$ • 10-year incidence of DDR: 6% versus 7.5%; HR 0.71 (0.55–0.93); $P = .01$
DA [54]	N = 1,860	• Postmenopausal • 67% LN-positive • Completed 2–3 years of tamoxifen	• Anastrozole for 3 additional years versus 6 additional years	• 5-year DFS: 83% versus 79% LN±: 84% versus 76%; HR 0.64 (0.46-0.89); P=0.007 T≥2 tumors: 82% versus 69%; HR 0.53 (0.53-0.82); P=0.003 • 5-year OS: 91% versus 90% • 5-year incidence of CLBC: 1.5% versus 3.3%
IDEAL [53]	N = 1,824	• Postmenopausal • 75% LN-positive • Completed 5 years of ET	• Letrozole for 2.5 additional years versus 5 additional years	• 5-year DFS: 152 versus 163 events • 5-year OS: 104 versus 96 events • 5-year incidence of CLBC: 3.1% versus 1.1%; HR 0.39 (0.19–0.81); $P = .01$
Ovarian function suppression				
SOFT [56]	N = 3,047	• Premenopausal • 85% HER2-negative • 35% LN-positive	• Tamoxifen versus • Tamoxifen-OFS versus • Exemestane-OFS	• 8-year DFS: 79% (T) versus 83% (T-OFS) versus 86% (E-OFS); HR 0.76 (0.62–0.93); $P = .009$ HER2-negative, prior chemotherapy: 72% versus 74% versus 83%; HR 0.62 (0.46–0.83) ≤35 years: 64% versus 73% versus 77%; HR 0.52 (0.31–0.87) • 8-year OS: 91.5% (T) versus 93% (T-OFS) versus 92% (E-OFS); HR 0.67 (0.48–0.92); $P = .01$
SOFT/TEXT [57]	N = 4,690	• Premenopausal • 86% HER2-negative • 42% LN-positive	• Exemestane-OFS versus • Tamoxifen-OFS	• 8-year DFS: 87% versus 83%; HR 0.77 (0.67–0.9); $P < .001$ • 8-year OS: 93% versus 93% • 8-year DDFS: 92% versus 90%; HR 0.80 (0.66–0.96); $P = .02$ HER2-negative, prior chemotherapy: SOFT: 79% versus 87%; HR 0.68 (0.48–0.95) TEXT: 85% versus 89%; HR 0.69 (0.5–0.93)

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Table 1 (*continued*)

Study	Number	Population	Study design	Outcomes
Adjuvant bisphosphonates				
EBCTCG meta-analysis [58]	N = 18,766	• 63% postmenopausal • 54% LN-positive • Most patients (97%) received 2–5 years of bisphosphonate	• Bisphosphonate versus control (either open-label or placebo)	• 10-year cumulative risk of recurrence: 26% versus 25% Postmenopausal: RR 0.86 (0.78–0.94); $P = .002$ • 10-year cum risk of DDR: 22% versus 20%; RR 0.92 (0.85–0.99), $P = .02$ Postmenopausal: RR 0.82 (0.74–0.92); $P = .0003$ • 10-year cum risk of bone recurrence: 9% vs. 8%; RR 0.83 (0.73–0.94); $P = .004$ Postmenopausal: RR 0.72 (0.60–0.86); $P = .002$ • 10-year breast cancer mortality: 18% versus 17%; RR 0.91 (0.83-0.99); $P = .04$ Postmenopausal: RR 0.82 (0.73–0.93); $P = .002$ • 10-year cum risk of bone fractures: 10% versus 9%, RR 0.85 (0.75–0.97); $P = .02$

BCFI = breast-cancer free interval; CLBC = contralateral breast cancer; DDFS = distant disease-free survival; DDR = distant disease recurrence; DFS = disease-free survival; EBCTCG = Early Breast Cancer Trialists Collaborative Group; ER = estrogen-receptor; ET = endocrine therapy; HER2 = human epidermal growth-factor receptor 2; HR+ = hormone receptor positive; HR = hazard ratio (95% confidence interval); LN = lymph node; RS = Oncotype-Dx 21-gene Recurrence Score; OFS = ovarian function suppression; OS = overall survival; RFS = recurrence free survival; RR = relative risk (95% confidence interval);

CLINICAL TRIALS

NSABP B20 [33] — NCT01446185 — Treatment Decision Impact of OncotypeDX in HR+, N- Breast Cancer Patients (SWITCH)
TAILORx [34] — NCT00310180 — Hormone Therapy With or Without Combination Chemotherapy in Treating Women Who Have Undergone Surgery for Node-Negative Breast Cancer (The TAILORx Trial)
MINDACT [40,41] — NCT00433589 — Genetic Testing or Clinical Assessment in Determining the Need for Chemotherapy in Women With Breast Cancer That Involves No More Than 3 Lymph Nodes (MINDACT)
aTTom [45,46] — NCT00003678 — Tamoxifen in Treating Women With Breast Cancer
ATLAS [44] — Cancer Research UK, UK Medical Research Council, SRCTN19652633. — Adjuvant Tamoxifen: Longer Against Shorter (ATLAS)
MA.17 [48] — NCT00897065 — Biomarkers in Predicting Response to Tamoxifen and Letrozole in Postmenopausal Women With Primary Breast Cancer Treated on Clinical Trial CAN-NCIC-MA17
NASBP B33 [49] — NCT00016432 – Exemestane in Treating Postmenopausal Women With Resected Stage I, Stage II, or Stage IIIA Breast Cancer Who Have Completed 5 Years of Tamoxifen
MA.17R [52] — NCT00754845 —, Letrozole in Breast Cancer Who Have Received 5 Years of Aromatase Inhibitor Therapy;
NSABP B42 [49–51] — NCT00382070 — Letrozole in Treating Postmenopausal Women Who Have Received Hormone Therapy for Hormone Receptor-Positive Breast Cancer
DATA [54] — NCT00301457 — Different Durations of Adjuvant Anastrozole Therapy After 2 to 3 Years Tamoxifen Therapy in Breast Cancer (DATA)
IDEAL [53] — NCT01249456 — Safety and Efficacy Study of Femara(Letrozole) as an Extended Adjuvant Treatment in Breast Cancer Patients
SOFT [56] — NCT00066690 — Suppression of Ovarian Function With Either Tamoxifen or Exemestane Compared With Tamoxifen Alone in Treating Premenopausal Women With Hormone-Responsive Breast Cancer (SOFT)
SOFT/TEXT [57] — NCT00066690 and NCT00066703 — Suppression of Ovarian Function With Either Tamoxifen or Exemestane Compared With Tamoxifen Alone in Treating Premenopausal Women With Hormone-Responsive Breast Cancer (SOFT) and Triptorelin With Either Exemestane or Tamoxifen in Treating Premenopausal Women With Hormone-Responsive Breast Cancer (TEXT)
EBCTCG, Early Breast Cancer Trialists Collaborative Group
Note: HR, 95%CI and *P*-values reported only if statistically significant

to confirm benefit in DFS with extended AI [53,54]. Overall, the data suggest that extended adjuvant AI provides modest DFS benefit, driven mainly by reduction in contralateral breast cancer. Benefits of extended AI therapy should also be weighed with higher rates of cardiovascular risk factors and osteoporotic fractures [55]. These studies are summarized in Table 1.

Ovarian suppression in premenopausal women

Ovarian functional suppression (OFS) by surgical or pharmacologic means may be considered for high-risk premenopausal women to reduce risk of recurrence (Table 1). The International Breast Study Group (IBCSG) commenced the SOFT and TEXT trials to evaluate OFS in addition to adjuvant ET for premenopausal women. In combined analysis of both trials, DFS was compared for 3 groups, exemestane-OFS versus tamoxifen-OFS versus tamoxifen alone. Results demonstrated that the addition of OFS to tamoxifen improved both DFS and OS compared to tamoxifen alone. Exemestane-OFS resulted in further improvement in DFS, but not OS, compared to tamoxifen-OFS. However, the largest magnitude of benefit was seen with use of OFS in patients with high risk of recurrence. Since OFS is associated with increased toxicity, it should be considered primarily for women who have received chemotherapy (should include large tumors, LN-positive, and high genomic risk) and younger women [56,57].

Adjuvant bisphosphonate

In addition to the effects on bone-mineral density, some studies have suggested that use of bisphosphonates may be associated with improved breast cancer survival in postmenopausal women. An EBCTCG meta-analysis (Table 1), which included a number of heterogeneous studies using different bisphosphonates and different schedules, demonstrated that the use of bisphosphonate reduced the risk of bone-only breast cancer recurrence in all patients and reduced the risk of breast cancer recurrence, distant metastases and breast cancer related deaths in postmenopausal women irrespective of HR status, tumor grade, nodal involvement or chemotherapy use [58]. Updated American Society of Clinical Oncology guidelines recommend consideration of adjuvant bisphosphonate, with either zoledronic acid for 3–5 years or clodronate for 2–3 years duration, for postmenopausal patients who are deemed candidates for adjuvant systemic therapy [59].

Targeted agents

Given the progression-free survival and OS benefits seen with cyclin-dependent kinase 4/6 inhibitors in advanced HR-positive breast cancer, these agents are currently being evaluated in the (neo) adjuvant setting in an attempt to reduce the rate of recurrence after definitive treatment for early stage HR-positive breast cancer. The Palbociclib Collaborative Adjuvant Study is an ongoing (NCT02513394) phase III trial assessing the addition of 2 years of palbociclib to 5 years of standard ET in stage II-III breast cancer [60]. Following a preplanned efficacy analysis, the investigators announced that this study is unlikely to show statistically significant improvement in IDFS. The New Adjuvant Trial with LEE study is an ongoing (NCT03701334) phase III trial of 3-year of ribociclib added to 5 years of standard ET [61].

Management of HER2-positive early-stage breast cancer

Patients with HER2-positive early stage breast cancer generally warrant treatment with chemotherapy in addition to anti-HER2 agents. Patients with stage II or III HER2-positive breast cancers are offered NACT for risk stratification by pCR, and consideration of adjuvant TDM1 with residual disease [31]. For patients with pCR following HER2-directed therapy, adjuvant trastuzumab (± pertuzumab) is recommended to complete 1 year of anti-HER2 therapy [6]. Patients with smaller, node-negative tumors may proceed with surgery as the initial treatment since they may be candidates for deescalated chemotherapy regimen with paclitaxel plus trastuzumab for 12 weeks follow by trastuzumab to complete 1 year of adjuvant anti-HER2 therapy [6,62,63]. The landmark trials for HER2-positive early stage disease are discussed below.

HER2-targeted therapy

Trastuzumab

Trastuzumab is a monoclonal antibody that binds the extracellular domain of HER2. The benefits of adding trastuzumab to adjuvant chemotherapy in patients with HER2-positive tumors have been demonstrated in several studies as summarized in Table 2. A 2012 meta-analysis showed improvement in DFS regardless of trastuzumab treatment duration or schedule [64]. Improvement in OS was seen only in patients treated for 12 months (HR 0.67, 95% CI 0.57–0.80) and concurrent administration of trastuzumab with chemotherapy (HR 0.64, 95% CI 0.53–0.76) [62]. Subsequent data has confirmed that the addition of trastuzumab to chemotherapy results in durable survival benefit in HER2-positive breast cancer. In combined analysis of North Central Cancer Treatment Group N9831 and NSABP B31 trials, the addition of trastuzumab to chemotherapy (doxorubicin and cyclophosphamide followed by paclitaxel with trastuzumab) resulted in 37% improvement in OS (HR 0.63, 95% CI 0.54–0.73) and 40% improvement in DFS (HR 0.60, 95% CI 0.53–0.68) compared to chemotherapy alone [65].

Various durations of adjuvant trastuzumab have been investigated and the current standard is 1 year. The HERA trial demonstrated no additional benefit with extension of trastuzumab to 2 years [66]. Results of 6-month versus 12-month of adjuvant trastuzumab are discordant. In the PHARE trial, 6-month of trastuzumab did not meet criteria for noninferiority; however, significantly more patients in the 12-month group experienced a cardiac event (5.7% *v* 1.9%, $P<$ .001) [67]. Similarly, in the Hellenic Oncology Research Group trial, 6-month of adjuvant trastuzumab failed to demonstrate noninferiority [68]. By contrast, in the PERSEPHONE trial, adjuvant trastuzumab for 6-months was found to be noninferior to 12-month. Furthermore, 6-month of therapy reduced cardiac events by 3% and reduced discontinuation rates by 5% [69]. The different outcomes of these trials may be attributed to variability in the prespecified non-inferiority criteria. Moreover, in the subset of the PERSEPHONE trial that mirrors contemporary practice with concurrent chemotherapy and trastuzumab, there was benefit for the 12-month versus 6-month duration (4-year DFS 93% *v* 89%, HR 1.53, 95% CI 1.16–2.01) [69]. Studies of trastuzumab for 9 weeks also failed to demonstrate noninferiority [70,71].

Randomized controlled trials establishing the benefit of trastuzumab in HER2-positive early stage breast cancer limited eligibility to women with node-positive or high-risk node-negative breast cancer. Limited information is available regarding low-risk node-negative cases (tumors <1-cm). In a recent meta-analysis of 7 studies involving 1,181 patients with T1a-bN0 HER2-positive breast cancer, patients treated with trastuzumab were less likely to experience disease recurrence than controls (OR 0.201, 95% CI 0.1–0.404). There was a trend toward reduction in distant recurrence, although results were not statistically significant (OR 0.328, 95% CI 0.082–1.311) [72]. Current National Comprehensive Cancer Network guidelines recommend considering use of adjuvant trastuzumab with chemotherapy in these patients after balancing risk of toxicities (such as cardiotoxicity) [6].

Pertuzumab

Pertuzumab is a monoclonal antibody that binds the extracellular dimerization domain of HER2 and prevents it from binding

Table 2
Landmark trials in HER2-positive early-stage breast cancer.

Study	Number	Population	Study Design	Outcomes
Trastuzumab				
HERA [66]	N = 5,099	• 57% LN-positive • 50% HR+ • Completed chemotherapy	• Observation (A) versus trastuzumab for 1-year (B) versus 2-year (C) (Cross-over allowed)	• 10-year DFS: 63% (A) versus 69% (B) versus 69% (C), HR, 0.76 (0.68–0.86); $P < .0001$ (A *v* B) • 10-year OS: 73% versus 79% versus 80%, HR 0.74 (0.64–0.86); $P < .0001$ (A *v* B) • 10-year incidence of cardiac events: 1% versus 5.4% versus 8.3%
PHARE [67]	N = 3,380	• 44.5% LN-positive • 58.1% HR+ • Completed at least 4 cycles of chemotherapy	• Trastuzumab for 1-year versus 6-months (Noninferiority margin 1.15)	• 2-year DFS: 94% versus 91%, HR 1.28 (1.05–1.56); P=0.29 • 2-year OS: 96% versus 95% 2-year incidence of cardiac events: 5.7% versus 1.9%, $P < .001$
HORG [68]	N = 481	• 79% LN-positive • 67% HR+ • Completed ddFEC followed by ddT for 4 cycles	• Trastuzumab concurrent with docetaxel for 1-year versus 6-month (Noninferiority margin 1.53)	• 3-year DFS: 96% versus 93%, HR 1.57 (0.86–2.10); $P = .137$ • No difference in OS • No difference in cardiotoxicity
PERSEPHONE [69]	N = 4,089	• 62% LN-positive • 69% HR+ • Completed chemotherapy	• Trastuzumab for 6-month versus 1-year (Noninferiority margin 3%)	• 4-year DFS: 89% versus 90%, HR 1.07 (0.93–1.24); $P = .011$ • 4-year OS: 95% versus 94%, HR 1.14 (0.95–1.37); $P = .001$ • 4-year incidence of clinical cardiac dysfunction: 8% versus versus 11%; $P = .00014$
Short-HER [71]	N = 1,254	• 56% LN-positive • 68% HR+ • Completed anthracycline-taxane chemotherapy	• Trastuzumab for 1-year versus 9-weeks (Noninferiority margin 1.29)	• 5-year DFS: 88% versus 85% • 5-year OS: 95% versus 95% • 5-year risk of cardiac events: 4% versus 13%, HR 0.32 (0.21–0.5); $P < .0001$
SOLD [70]	N = 2,174	• 60% LN-negative • 66% ER-positive • Completed docetaxel plus trastuzumab (9 weeks) followed by FEC	• No additional trastuzumab versus 1-year (Noninferiority margin 1.3)	• 5-year DFS: 88% versus 90.5% • 5-year OS: 95% versus 96% • 5-year cum incidence of cardiac events: 2% versus 4%; $P = .01$
Pertuzumab				
NEOSPHERE [73,74]	N = 417	• 70% LN-positive • 47% ER-positive	• Neoadjuvant TH versus THP versus HP versus Pertuzumab plus docetaxel	• pCR rate: 46% (THP) versus 29% (TH), $P = .141$ • 3-year DFS : 85% versus 92% • 3-year PFS : 86% versus 90%
TRYPHAENA [75,76]	N = 225	• Tumors >2-cm • LVEF ≥55% at baseline	• FEC+HP, THP (A) versus FEC, THP (B) versus TCHP (C)	• Incidence of symptomatic LVSD: 0% (A) versus 2.7% (B) versus 0% (C) • Incidence of LVEF decline ≥10% from baseline: 5.6% (A) versus 5.3% (B) versus 3.9% (C)
APHINITY [77]	N = 4,805	• 63% LN-positive • 36% HR+ • Receiving adjuvant chemotherapy plus trastuzumab for 1-year	• Combination with pertuzumab versus placebo	• 3-year IDFS: 94% versus 93%, HR 0.81 (0.66-1.00); $P = .045$ LN±: 92% versus 90%; HR 0.77 (0.62–0.96); $P = .02$ LN-negative: 97.5% versus 98% • 3-year OS: 96% versus 96% • Low overall incidence of cardiac events
Trastuzumab emtansine (T-DM1)				
KATHERINE [31]	N = 1,486	• Tumors ≥1-cm • 72% HR+ • Residual disease	• T-DM1 versus • Trastuzumab	• 3-year IDFS: 88% versus 77%, HR 0.5 (0.39–0.64); $P < .001$ • 3-year DDFS: 90% versus 83%, HR 0.6 (0.45–0.79) • 3-year OS: 56 versus 42 deaths
Other anti-HER2 therapy				
NeoALTTO [79]	N = 455	• Neoadjuvant anti-HER2 in combination with paclitaxel followed by adjuvant FEC followed by anti-HER2 to complete 1-year	• Neoadjuvant • Lapatinib (A) versus Trastuzumab (B) versus Lapatinib plus trastuzumab (C)	• pCR rate: 20% versus 27% versus 44% • 3-year EFS: 78% versus 76% versus 84% Pts with pCR: HR 0.38 (0.22–0.63); $P = .0003$ • 3-year OS: 93% versus 90% versus 95% Pts with pCR: HR 0.35 (0.15–0.70); $P = .005$

(*continued on next page*)

Table 2 (*continued*)

Study	Number	Population	Study Design	Outcomes
ALTTO [80]	N = 8,381	• 40% LN-negative • 57% HR+ • Completed anthracycline and receiving paclitaxel with anti-HER2 therapy	• Adjuvant Lapatinib plus trastuzumab (L+T) versus Trastuzumab (T)	• 4-year DFS: 88% (L+T) versus 86% (T) • 4-year OS: 95% (L+T) versus 94% (T) • Serious AE: 21% (L+T) versus 14% (T) • Treatment discontinued due to AE: 23% (L+T) versus 8% (T)
ExteNET [81]	N = 2,840	• 77% LN-positive • 57% HR+ • Completed neoadjuvant or adjuvant chemotherapy plus trastuzumab (T)	• Oral neratinib versus placebo	• 5-year IDFS: 90% versus 88%, HR 0.73 (0.57–0.92); $P = .008$ HR±: HR 0.6 (0.43–0.83) HR-negative: HR 0.95 (0.66–1.35) Completion of T ≤1 year: HR 0.70 (0.54–0.90) Completion of T ≥1 year: HR 1.00 (0.5-0.94) • Grade ≥3 diarrhea: 40% versus 2% • Treatment discontinued due to AE: 28% versus 5%

AE = adverse events; AC = doxorubicin, cyclophosphamide; ACT = doxorubicin, cyclophosphamide, taxane; ACTH = doxorubicin, cyclophosphamide, taxane plus trastuzumab; DDFS = distant disease-free survival; ddT = dose-dense docetaxel; ddFEC = dose-dense FEC, dose-dense 5-fluorouracil + epirubicin + cyclophosphamide; DFS = disease-free survival; EFS = event-free survival; FEC = 5-fluorouracil + epirubicin + cyclophosphamide; HER2 = human epidermal growth factor receptor 2; HP = trastuzumab + pertuzumab; HR+ = hormone receptor positive; HR = hazard ratio (95% confidence interval); IDFS = invasive disease-free survival; LN = lymph node; LVEF = left ventricular ejection fraction; LVSD = left ventricular systolic dysfunction; OS = overall survival; pCR = pathologic complete response; PFS = progression-free survival; TCH = taxane, carboplatin, trastuzumab; TCH(P) = taxane, carboplatin, trastuzumab (pertuzumab); T-DM1 = trastuzumab emtansine; TH = taxane, trastuzumab; THP = taxane, trastuzumab and pertuzumab

CLINICAL TRIALS:

HERA [66] — NCT00045032 — Herceptin (Trastuzumab) in Treating Women With Human Epidermal Growth Factor Receptor (HER) 2-Positive Primary Breast Cancer
PHARE [67] — NCT00381901 — Trastuzumab for 6 Months or 1 Year in Treating Women With Nonmetastatic Breast Cancer That Can Be Removed By Surgery
HORG **[68]** — NCT00615602 — Six versus 12 months of adjuvant trastuzumab in combination with dose-dense chemotherapy for women with HER2-positive breast cancer: a multicenter randomized study by the Hellenic Oncology Research Group (HORG)
PERSEPHONE [69] — NCT00712140 — Trastuzumab in Treating Women With HER2-Positive Early Breast Cancer
Short-HER [71] — NCT00629278] —Combination Chemotherapy and Trastuzumab in Treating Women With Stage I, Stage II, or Stage III HER2-Positive Breast Cancer
SOLD [70] — NCT00593697] — The Synergism Or Long Duration (SOLD) Study
NEOSPHERE [73,74] — NCT00545688 — A Study of Pertuzumab in Combination With Herceptin in Patients With HER2 Positive Breast Cancer.
TRYPHAENA [75,76] — NCT00976989 — A Study of Pertuzumab in Combination With Herceptin and Chemotherapy in Participants With HER2-Positive Breast Cancer
APHINITY [77] — NCT01358877 — A Study of Pertuzumab in Addition to Chemotherapy and Trastuzumab as Adjuvant Therapy in Participants With Human Epidermal Growth Receptor 2 (HER2)-Positive Primary Breast Cancer (APHINITY)
KATHERINE [31] — NCT01772472 — A Study of Trastuzumab Emtansine Versus Trastuzumab as Adjuvant Therapy in Patients With HER2-Positive Breast Cancer Who Have Residual Tumor in the Breast or Axillary Lymph Nodes Following Preoperative Therapy (KATHERINE)
NeoALTTO [79] — NCT00553358 — Neo ALTTO (Neoadjuvant Lapatinib and/or Trastuzumab Treatment Optimisation) Study
ALTTO [80] — NCT00490139 — ALTTO (Adjuvant Lapatinib And/Or Trastuzumab Treatment Optimisation) Study; BIG 2-06/N063D
ExteNET [81] — NCT00878709 — Study Evaluating The Effects Of Neratinib After Adjuvant Trastuzumab In Women With Early Stage Breast Cancer (ExteNET)

to itself of other members of the epidermal growth factor receptor family. It is administered in combination with trastuzumab in patients with high-risk HER-2 positive breast cancer. Neoadjuvant dual anti-HER blockade with pertuzumab and trastuzumab was found to improve pCR rate by 16.8% (45.8 *v* 29%, $P = .01$) compared with single-agent trastuzumab combined with chemotherapy in the NeoSphere trial. However, there was no difference in DFS or progression-free survival after 3-year of follow-up [73,74]. The TRYPHAENA study was designed to assess the cardiac safety of dual anti-HER2 blockade with chemotherapy. In secondary efficacy analysis, 3-year DFS and OS was comparable between chemotherapy regimens and significant improvement in DFS was seen for patients who had pCR to NACT (HR 0.27, 95% CI 0.11–0.64) [75,76]. Among patients with LN-positive breast cancer in the APHINITY trial, those randomized to receive adjuvant pertuzumab with trastuzumab for 1 year following chemotherapy had improved 3-year IDFS by 1.8% (92 *v* 90.2%, HR 0.77, 95% CI 0.62–0.96) [77]. Both the APHINITY and TRYPHAENA studies demonstrated no increase in rates of cardiac events with the addition of pertuzumab. Overall, non-anthracycline containing regimens had lower rates of decline in left ventricular ejection fraction function and no patients developed symptomatic left ventricular systolic dysfunction [75–77]. These studies are summarized in Table 2.

Trastuzumab emtansine

Trastuzumab emtansine (T-DM1,KADCYLA) is an antibody-drug conjugate of trastuzumab and emtansine, a microtubule inhibitor. T-DM1 retains trastuzumab activity while providing intracellular delivery of DM1 into HER2-expressing cells. The risk of recurrence or death is higher among patients with residual disease at surgery than among patients with a pCR following NACT for HER2-postiive breast cancer [27–29]. In the KATHERINE trial (Table 2), adjuvant treatment with T-DM1 improved 3-year IDFS by 11.3% (88.3 *v* 77%, HR 0.50, 95% CI 0.39–0.64) and reduced 3-year cumulative risk of distant recurrence by 5.8% (10.5% *v* 16.3%, HR 0.60, 0.45–0.79) among patients with residual disease following NACT compared to adjuvant trastuzumab [31]. Thus, switching adjuvant anti-HER2 therapy to T-DM1 is recommended for patients with residual disease after NACT [6].

T-DM1 has been explored in the adjuvant setting for stage I breast cancer, but there are concerns over tolerability and limited follow-up data. In the phase II ATEMPT trial, patients were randomized to adjuvant T-DM1 or paclitaxel + trastuzumab (TH). The study was not powered to compare DFS between treatment groups, but 3-year DFS was 97.7% (95% CI 96.2–99.3) for patients treated with T-DM1 and 92.8% (95% CI 87.7–98.1) for patients treated with TH. However, T-DM1 was not associated with fewer toxicities and 17% of patients receiving T-DM1 discontinued treatment because of toxicity, compared to 6% receiving TH [78].

Other anti-HER2 therapy

The role of dual blockage with agents other than pertuzumab remains unclear. Neoadjuvant dual anti-HER2 blockade with trastuzumab and lapatinib also improved pCR rate by 17%

(44 *v* 27%) compared to single-agent trastuzumab plus chemotherapy in the NeoALTTO trial. However, only those with pCR had significantly improved 3-year EFS (HR 0.38, 95% CI 0.22–0.63) and OS (HR 0.35, 95% CI 0.15–0.70) [79]. In ALTTO, the addition of lapatinib to adjuvant trastuzumab did not yield additional benefit in 4-year DFS or OS [80]. Neratinib has been shown to decrease recurrence rates when used in the adjuvant setting following treatment with single-agent trastuzumab, particularly in patients with large tumors that are also ER positive. In the ExteNET study, women randomized to neratinib after completing a year of adjuvant trastuzumab had improved 5-year IDFS by 2.5% (90.2 *v* 87.7%, HR 0.73, 95% CI 0.57–0.92). There was a trend toward greater improvements for those with HR-positive disease compared with HR-negative disease. However, many patients ended treatment early due to diarrhea. The frequency of grade 3 to 4 diarrhea with neratinib was 40% without diarrhea prophylaxis versus 2% among those receiving placebo [81]. There are no data on the safety or efficacy of neratinib in patients whose adjuvant therapy included pertuzumab, further limiting its clinical utility. These studies are summarized in Table 2.

Choice of chemotherapy

Data regarding the combination of anthracycline-based chemotherapy plus trastuzumab come largely from NSABP B31 and N9831. In combined analysis at 8.4 years of median follow-up, the addition of adjuvant trastuzumab (concurrent with taxane) to anthracycline-taxane based chemotherapy resulted in significantly improved 10-year DFS by 11.5% (73.7 *v* 62.2%, HR 0.60, 95% CI 0.53–0.68) and 10-year OS by 8.8% (84% *v* 75.2%, HR 0.63, 95% CI 0.54–0.73) [82]. However, the cumulative incidence of cardiac toxicities were 4.0% in B31 and 3.4% in N9831 for patients receiving both trastuzumab and anthracycline [83–85].

Due to cardiotoxicity with anthracyclines and trastuzumab, non-anthracycline-based regimens were investigated. In the BCIRG-006 trial of women with LN-positive or high-risk LN-negative disease, adriamycin + cyclophosphamide + paclitaxel + trastuzumab (ACTH) demonstrated a trend toward improved DFS and OS but was associated with higher rates of heart failure compared with docetaxel + carboplatin + trastuzumab (TCH) (2% *v* 0.4%, $P < .001$) [86]. However, this study was not powered to compare outcomes between ACTH and TCH. The TRAIN-2 study showed similar pCR rates for patients with stage II-III breast cancer receiving trastuzumab and pertuzumab concurrently with chemotherapy whether they were randomized to receive anthracycline-containing or non-anthracycline-containing regimens (67% *v* 68%, $P = .95$) [87]. These data suggest that anthracyclines may be avoided in favor of the TCH regimen, particularly for patients with risk factors for cardiotoxicity (ie, older age, hypertension). For patients with stage II-III breast cancer, EA1181 is an ongoing trial (NCT04266249) to determine if pCR with taxane-based chemotherapy regimen docetaxel + trastuzumab + pertuzumab, (THP) allows de-escalation of adjuvant therapy without compromising 3-year relapse-free survival. Patients with pCR will complete 1-year of dual anti-HER2 blockade trastuzumab + pertuzumab (HP) while patients with residual disease may receive AC or TDM1 per investigator's choice [88].

In the WSG-ADAPT phase II study, neoadjuvant therapy with HP was compared with combination anti-HER2 therapy plus paclitaxel for 12 weeks (THP). The study failed to demonstrate non-inferiority in pCR rates with dual anti-HER2 blockade alone compared to combination with chemotherapy, especially because of the very high pCR rate in patients treated with the THP regimen at 90.5% (95% CI 77.4–97.3). Exploratory results suggested poor pCR (8.3%) in patients failing to achieve response after 1 cycle of dual blockade, which was much lower than in others (early responders: 44.7%, unclassifiable: 42.9%). This study suggests a role for further de-escalation of chemotherapy in patients with HER2-positive and ER-negative disease [89]. For patients with smaller LN-negative tumors, TH is usually preferred over TCH or ACTH although the regimens have never been directly compared. A single-arm phase II trial evaluated trastuzumab plus weekly paclitaxel in patients with LN-negative tumors ≤3cm (majority were less than 1-cm). Overall toxicity was minimal and long-term outcomes were excellent with 7-year DFS of 93% (95% CI 90.4–96.2) and 7-year OS of 95% (95% CI 95.9–99.1) [62,63].

Management of Triple-negative early-stage breast cancer

Triple negative breast cancer (TNBC) lacks expression of hormone receptors and HER2. As these patients have a higher risk of relapse compared to other breast cancer subtypes and are not candidates for targeted agents, chemotherapy is typically recommended. Chemotherapy regimens including anthracyclines and taxanes remain the standard regimens for TNBC. As pCR is associated with improvement in DFS [27–29], NACT is the preferred approach in most patients with tumors >2-cm or LN-positive disease because of available adjuvant regimens for those with residual disease [6,30]. Ongoing studies are evaluating the benefit of incorporating carboplatin and immunotherapy as (neo) adjuvant therapy patients with early-stage TNBC and have demonstrated some promising early results, however, the benefit has yet to be confirmed. These studies are summarized in Table 3.

Chemotherapy

Carboplatin

In high-risk patients with TNBC, the addition of carboplatin to paclitaxel and anthracycline-containing NACT improves pCR rates. Multicenter trials show pCR rates of 22%–39% for anthracycline-taxane-containing regimens without carboplatin and 53%–60% for similar regimens with the addition of carboplatin. In the GeparSixto, Cancer and Leukemia Group B 40603, and BrighTNess trials, the addition of carboplatin to standard chemotherapy increased the pCR rate by 16.6, 14, and 27%, respectively [90–95]. However, none of the studies were designed to determine definitively whether the addition of carboplatin to NACT improves DFS or OS. GeparSixto did report a significant improvement in DFS by 10% with the addition of weekly carboplatin to standard chemotherapy after a median follow-up of 47.3 (range 1.7–62.8) months (86 *v* 76%; HR 0.56, 95% CI 0.34–0.93), and a trend toward improvement in 3-year OS (92 *v* 86%; HR 0.60, 95% CI 0.32–1.12) [90–92]. By contrast, the Cancer and Leukemia Group B 40603 study did not demonstrate improved 5-year EFS or OS for the addition of carboplatin to standard NACT [93–94]. Survival outcomes from BrighTNess have not been reported.

Although platinum-based therapy may be beneficial in women with hereditary breast cancer gene (BRCA)1/2 mutations given defects in DNA damage repair, trials report that patients without a germline BRCA mutation exhibit a greater increase in pCR rate than those whose tumors harbor BRCA-mutations [91,92,95]. In BrighTNess, the addition of carboplatin increased the pCR rate in patients whose tumors were found to be wild type for BRCA- (29%–59%) more than in patients whose tumors harbored BRCA mutations (41%–50%) [95]. Similarly, in GeparSixto, 3-year DFS was greater with the addition of carboplatin in patients whose tumors were found to be wild type for BRCA (74%–85%) compared to those whose tumors had BRCA mutations (82%–86%) [91,92].

Capecitabine

Meta-analysis shows that substitution of standard chemotherapy with capecitabine has not improved OS [96]. However, in patients with residual disease after NACT, adjuvant capecitabine has

Table 3
Landmark trials in triple negative early-stage breast cancer.

Study	Number	Population	Study Design	Outcomes
Neoadjuvant carboplatin				
GeparSIxto (GBG 66) [91,92]	N = 315	• Stage II-III • Receiving paclitaxel, non-pegylated doxorubicin, and bevacizumab	• Carboplatin versus No Carboplatin	• pCR rate: 53.5% versus 37%, OR 1.94 (1.24–3.04); $P = .005$ Without gBRCA1/2 mutation: 55% versus 36%, OR 2.14 (1.28–3.58); $P = .004$ • 3-year DFS: HR 0.55 (0.32–0.95); $P = .03$ Without gBRCA1/2 mutation: 85% versus 73.5%, HR 0.53 (0.29–0.96); $P = .04$
CALGB 40603 [93,94]	N = 454	• Stage II-III • 58% LN-positive • Receiving Paclitaxel plus study agents, then ddAC	• Carboplatin and/or bevacizumab	• pCR rate: 60% versus 46%; OR 1.76; $P = .002$
BrighTNess [95]	N = 634	• Stage II-III • 42% LN-positive • Receiving paclitaxel plus study agents, then AC	• Carboplatin plus veliparib (A), Carboplatin plus placebo (B), Veliparib plus placebo (C), Both placebo (D)	• pCR rate: 58% (B) versus 31% (D); $P <$ .0001 gBRCA1/2 mutation: 50% versus 41% Without gBRCA1/2 mutation: 59% versus 29%
Adjuvant capecitabine				
CREATE-X [30]	N = 910	• Stage I-IIIB • 61% LN-positive • Residual disease • 32% TNBC	• Adjuvant capecitabine for 8 cycles versus control	• 3-year DFS: 83% versus 74%; HR 0.7 (0.53–0.92), $P = .01$ TNBC: 70% versus 56%; HR 0.58 (0.39–0.87) • 3-year OS: 94% versus 89%; HR 0.59 (0.39–0.90), $P = .01$ TNBC: 79% versus 70%; HR 0.52 (0.30–0.90)
SYSUCC-001 [98]	N = 434	• Completed standard therapy	• Adjuvant capecitabine for 1-year versus observation	• 5-year DFS: 83% versus 73%; HR 0.63 (0.42–0.96); $P = .027$ • 5-year DDFS: 85% versus 76%; HR 056 (0.37–0.90); $P = .016$ • 5-year OS: 85% versus 81%
GEICAM/2003-11_CIBOMA/2004-01 [97]	N = 876	• LN-positive or node-negative with tumor >1cm • 44% LN-positive • Completed anthracycline or taxane-based therapy	• Adjuvant capecitabine for 8 cycles versus observation	• 5-year DFS: 80% versus 77% Non-basal phenotype: 83% versus 73%, HR 0.53 (0.31–0.91); $P = .022$ • 5-year OS: 87% versus 87.6% Non-basal phenotype: 89.5% versus 80%, HR 0.42 (0.21–0.81); $P = .0095$
Immunotherapy				
KEYNOTE-522 [101]	N = 602	• Stage II-III • 51% LN-positive • Receiving study agent with NACT; adjuvant study agent (up to 9 cycles) • 82% PDL1-positive	• Neoadjuvant and adjuvant • Pembrolizumab versus placebo	• pCR rate: 65% versus 51%; $P <.001$ PDL1-positive: 69% versus 55% LN-positive: 65% versus 44% • 18-month EFS: 91% versus 85%; HR 0.63 (0.43–0.93)

AC = doxorubicin + cyclophosphamide; DFS = disease-free survival; ddAC = dose-dense doxorubicin + cyclophosphamide; DDFS = distant disease-free survival; EFS = event-free survival; gBRCA1/2 = germline mutation in BRCA1 or BRCA2 tumor suppressor genes; HR = hazard ratio (95% confidence interval); LN = lymph node; NACT = neoadjuvant chemotherapy; OR = odds ratio (95% confidence interval); OS = overall survival; pCR = pathologic complete response; PDL1 = programmed death-ligand 1; TNBC = triple negative breast cancer;

CLINICAL TRIALS:

GeparSIxto (GBG 66) [91,92] — NCT01426880 — Addition of Carboplatin to Neoadjuvant Therapy for Triple-negative and HER2-positive Early Breast Cancer (GeparSixto)

CALGB 40603 [93,94] — NCT00861705 — Paclitaxel With or Without Carboplatin and/or Bevacizumab Followed by Doxorubicin and Cyclophosphamide in Treating Patients With Breast Cancer That Can Be Removed by Surgery

BrighTNess [95] — NCT02032277 — A Study Evaluating Safety and Efficacy of the Addition of ABT-888 Plus Carboplatin Versus the Addition of Carboplatin to Standard Chemotherapy Versus Standard Chemotherapy in Subjects With Early Stage Triple Negative Breast Cancer

CREATE-X [30] — UMIN Clinical Trials Registry number, UMIN000000843 — Capecitabine for Residual Cancer as Adjuvant Therapy

SYSUCC-001 [98] — NCT01112826 — Efficacy of Capecitabine Metronomic Chemotherapy to Triple-negative Breast Cancer (SYSUCC-001)

GEICAM/2003-11_CIBOMA/2004-01 [97] — NCT00130533 — Maintenance Treatment With Capecitabine Versus Observation in Breast Cancer Patients

KEYNOTE-522 [101] — NCT03036488 — Study of Pembrolizumab (MK-3475) Plus Chemotherapy versus Placebo Plus Chemotherapy as Neoadjuvant Therapy and Pembrolizumab versus Placebo as Adjuvant Therapy in Participants With Triple Negative Breast Cancer (TNBC) (MK-3475-522/KEYNOTE-522)

Note: HRs and associated 95% confidence intervals and *P*-value only reported if statistically significant

been shown to improve both DFS and OS. In the CREATE-X trial, patients with HER2-negative breast cancer (including 32% with TNBC) and residual disease after NACT were randomized to 6–8 cycles of capecitabine or no further chemotherapy. Patients receiving capecitabine had improved 5-year IDFS by 6% (74% *v* 68%, HR 0.70, 95% CI 0.53–0.92) and 5-year OS by 5% (89% *v* 84%, HR 0.59, 95% CI 0.39–0.90), and in subgroup analysis this effect was drive by patients with TNBC [26]. However, subsequent studies (SYSUCC-001 and GEICAM/2003-11_CIBOMA/2004-01) incorporating maintenance capecitabine following standard local and systemic treatments have not shown any significant improvements in OS [97,98].

Immunotherapy

Immunotherapy is not yet approved in early stage TNBC, and recent studies (GeparNuevo and I-SPY2) evaluating the addition of immunotherapy to NACT demonstrate effects on pCR [99,100]. In KEYNOTE-522, the addition of pembrolizumab to NACT regimens (taxane-platinum and anthracycline-combination) improved pCR rates by 13.6% (64.8% *v* 51.2%, $P<.001$) and EFS by 6% (91.3% *v* 85.3%, HR 0.63, 95% CI 0.43–0.93) after 15.5 months of median follow up regardless of programmed cell death ligand 1 status [101]. There are major limitations in this study including the lack of dose dense AC and use of carboplatin––both of which have been proven to improve OS; with the use of carboplatin also controversial as it is not known if this is beneficial to all patients with TNBC. Indeed, this 5-drug regimen was extremely toxic with 77% grade 3 or higher adverse events and fatalities seen in both arms. Further follow up is needed, and identifying those who truly require this aggressive regimen is critical to prevent overtreatment.

Healthy lifestyle

Lifestyle modifications can improve mental and physical health in patients with early breast cancer. Observational data suggests that exercise, weight management, and minimization of alcohol intake are also associated with decreased risk of disease recurrence and death in breast cancer survivors.

Diet

The impact of dietary modification alone on breast cancer outcomes is unclear. After 5-year of follow-up in the Women's Intervention Nutrition Study study, relapse events were 24% lower in women randomized to a low-fat dietary intervention compared to the control group (96/975 *v* 181/1462, HR 0.76, 95% CI 0.60–0.98) with greater effect among the subgroup with ER-negative cancers (28/205 *v* 59/273, HR 0.58, 95% CI 0.37–0.91) [102]. After 15 years of follow-up, death rates were numerically but not statistically lower in the intervention group compared with control group (13.6% *v* 17%, respectively). However, in the subgroup with ER-negative cancers, there was a 36% reduction in mortality in the intervention group compared to the control group [103]. After 7-year of follow-up in the Women's Healthy Eating and Living (WHEL) study, there was no difference in breast cancer recurrence or overall mortality between women randomized to the diet intervention (low in fats and high in fruits, vegetables, and fiber) compared to the control group [104]. The differences in outcomes between these studies may be in part attributed to the weight loss experienced by participants in Women's Intervention Nutrition Study and the longer enrollment period and inclusion of higher-risk patients in Women's Healthy Eating and Living.

Weight loss

Weight control and physical activity have also been showed to improve quality of life and reduce common symptoms among cancer survivors including sexual dysfunction, neuropathy, cardiotoxicity, chronic fatigue, and lymphedema [105]. Some trials have evaluated the feasibility and benefits of weight loss in women with breast cancer. In the Lifestyle Intervention in Adjuvant Treatment of Early Breast Cancer study, postmenopausal women with HR-positive breast cancer randomized to a two-year telephone-based weight loss intervention had greater weight loss from baseline compared to usual care (−5.4% *v* -0.7% at 6 months; −3.7% *v* -0.4% at 2 years, $P<.001$) [106]. In the Exercise and Nutrition to Enhance Recovery and Good Health for You trial, women with a history of breast cancer randomized to a group-based weight loss program lost more weight than the control group who received dietitian counseling and print materials (−6.0% *v* −1.5% at 1-year; −3.7% *v* −1.3% at 2-year, $P< .001$) [107]. However, studies are needed to determine if weight loss improves survival outcomes. The Breast Cancer Weight Loss trial (NCT02750826) is ongoing and will assess the impact of a 2-year telephone-based weight loss intervention on IDFS women with stage II-III breast cancer who are overweight or obese [108].

Physical activity

Observational studies suggest that breast cancer survivors who participate in moderate physical activity have improved outcomes compared with survivors who are less active. In a meta-analysis of 16 studies, a 48% reduction in overall mortality (RR 0.52, 95% CI 0.42–0.64) and 28% reduction in breast cancer mortality (RR 0.72, 95% CI 0.60–0.85) was seen for the highest versus lowest level of postdiagnosis physical activity. There was a 24% (95% CI 11–36%) reduction in overall mortality for each 10 metabolic equivalent task-hour/week increase in postdiagnosis physical activity (equivalent to 150 minutes/week of at least moderate intensity activity) [109]. Breast cancer survivors who increased their activity by any level pre- to postdiagnosis had a lower risk of overall mortality (RR 0.61, 95% CI 0.42–0.80) compared with survivors who did not change their activity level [109].

Conclusions

Decades of breast cancer research have led to significant advances in the management of patients with early stage breast cancer with systemic therapy. Treatment planning should consider tumor characteristics, particularly hormone receptor and HER2 status. Patients with HR-positive disease require individualized therapy recommendations incorporating tumor characteristics, prognostic and predictive genomic assays and estimated benefit of therapies. Patients with HER2-positive and TNBC generally have more aggressive disease and neoadjuvant therapies can be used to risk stratify and maximize the opportunity for cure. We have presented the landmark trials which have shaped the current standard of care for patients with early stage breast cancer, including some ongoing studies which will likely change the future treatment paradigm for this disease.

Declaration of competing interest

Dr Whitney Hensing has no disclosures. Dr Cesar Santa-Maria has research funding from Pfizer, Astrazeneca, Novartis, Bristol Meyers Squibb and has severed on advisory boards for Bristol Meyers Squibb, Genomic Health, Seattle Genetics, Athenex, Halozyme, and Polyphor. Dr Lindsay L. Peterson has no disclosures. Dr Jennifer Sheng has no disclosures.

Author contributions

JS, CS: Conceptualization. All authors: Writing of original draft, review, and editing.

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