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Indications for Neoadjuvant Systemic Therapy for Breast Cancer

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Keywords

• Neoadjuvant systemic therapy • Adjuvant systemic therapy • Breast cancer

Key points

- Neoadjuvant and adjuvant systemic therapies offer similar benefits in terms of overall and disease-free survival.
- Neoadjuvant systemic therapy (NST) enables downstaging of the tumor enhancing the surgical treatment options.
- NST reduces the axillary disease burden facilitating less extensive surgery of the axilla.
- Response to NST is a strong prognostic indicator and guides adjuvant treatment planning.
- Certain molecular subtypes of breast cancer respond better to NST, reflecting the need for careful selection of patients who can benefit the most from NST.

INTRODUCTION

Neoadjuvant systemic therapy (NST) was first used in patients with unresectable, advanced, or inflammatory breast cancer with the goal of shrinking the primary tumor, before the planned oncologic resection [1–3]. More recently, NST has been used to convert some patients presenting with stage II–III breast cancer deemed to require a mastectomy to candidates for breast-conserving therapy (BCT) by downsizing the volume of disease [4,5]. Decreasing the

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size of a primary breast cancer is often used to justify administration of systemic therapy in the neoadjuvant rather than the adjuvant setting, especially in patients in whom the need for adjuvant therapy is not in question. The main goals of NST are to reduce mortality from breast cancer, to improve surgical options, and to acquire early information on response of the tumor [6].

This article provides an overview of the landmark NST trials in patients with operable breast cancer, discusses the goals for NST, and provides an update on NST by tumor phenotype. Throughout this overview, the authors discuss the research possibilities NST provides and the future directions this may lead.

LANDMARK NEOADJUVANT SYSTEMIC THERAPY TRIALS

The first description of NST (initially referred to as primary chemotherapy) in patients with operable breast cancer was by Jacquillat and colleagues [7,8] in 1983. These pioneers in NST treated 143 stage I–III patients with polychemotherapy and reported a clinical complete response (cCR) in 30% of patients. This initial phase 2 trial spawned several prospective, randomized phase 3 clinical trials.

The first North American NST trial in patients with operable breast cancer was the National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial, a phase 3 trial designed to evaluate differences in neoadjuvant and adjuvant chemotherapy [9]. Between 1988 and 1993, 1523 patients with operable breast cancer were randomized to receive either neoadjuvant or adjuvant adriamycin and cyclophosphamide (AC). In the neoadjuvant group, the overall response rate (ORR) was 80%; the cCR rate was 36%, and the pathologic complete response (pCR) rate was 13%. For the entire cohort, more patients treated neoadjuvantly (67.8%) underwent successful BCT as compared with those treated adjuvantly (59.8%). Among the cohort of patients with tumors larger than 5 cm, 22% underwent breast conservation compared with 8% in the adjuvant therapy group. However, more importantly, with a median follow-up of 5 years [9] and 9 years [10], there was no difference in the disease-free survival (DFS) and overall survival (OS) between the 2 groups [9].

In Europe, the European Organization for Research and Treatment of Cancer conducted trial 10902 [11] in 698 patients with operable breast cancer using neoadjuvant or adjuvant fluorouracil, epirubicin, and cyclophosphamide. Patients receiving neoadjuvant therapy had a 49% ORR, 7% cCR, and 1.7% pCR rate. With median follow-up of 10 years, there is no difference in OS, DFS, or locoregional recurrences [11,12].

The NSABP-B27 trial was designed to evaluate the effect of adding docetaxel (T) to AC in both a neoadjuvant and an adjuvant setting. Between 1995 and 2000, 2411 patients were randomized to 3 arms, including (1) preoperative AC followed by surgery, (2) preoperative AC followed by T and then surgery, and (3) AC followed by surgery followed by T. The addition of T preoperatively to AC significantly increased the proportion of patients having a pCR compared with preoperative AC alone (26% vs 13%). There was no significant difference in OS or DFS between treatment arms [13].

Collectively, these 3 anthracycline-based NST trials demonstrated the order of therapy had no impact on OS or DFS and was safe for patients with operable breast cancer. Furthermore, these 2 trials set the stage for all subsequent NST trials. Preoperative chemotherapy has facilitated the increased use of BCT secondary to tumor downsizing without any increase in locoregional recurrence rates, establishing the safety and efficacy of NST. These clinical trials have set the benchmark for increased use of NST in patients with operable breast cancer.

GOALS OF NEOADJUVANT SYSTEMIC THERAPY

Impact on local-regional therapy

Multiple, prospective, randomized trials have demonstrated the use of NST to convert patients determined to need a mastectomy at presentation into candidates for BCT. However, multiple factors contribute to the candidacy of the patient for BCT, and it is imperative to be cognizant of other factors that may decrease the feasibility/success of BCT in patients, such as ratio of tumor size to native breast size, extent of microcalcifications multicentric tumors, lobular histology, and the ability of the patient to tolerate radiation therapy [14].

When discussing the surgical management for breast cancer, an important consideration is the tumor size to native breast size. Thus, an established benefit of NST is to potentially decrease the size of the index cancer and reduce the extent of surgery required to achieve tumor-free surgical margins. Patients with operable tumors may choose NST to facilitate adequate tumor resection with BCT, with the goal of obtaining negative margins, potentially removing less tissue, and simultaneously providing an improved cosmetic result. Another consideration in tumor to breast size is the extent of suspicious malignant-appearing microcalcifications. Radiographically, NST reduces the size of spiculated masses, but does very little to malignant-appearing microcalcifications. Because of the possibility of residual disease, these malignant-appearing microcalcifications must be removed at the time of surgery. Thus, the patient may or may not be an ideal BCT candidate depending on the extent of microcalcification to breast ratio.

Multicentric, synchronous ipsilateral breast cancers have been associated with increased risk of locoregional recurrence with BCT, and mastectomy is recommended for these patients [15]. Lobular histology is associated with larger underlying breast cancers, and for women with lobular histology and dense breast tissue, MRI has been shown to be effective in helping to delineate the extent of disease. Given these considerations, some patients with lobular pathologic condition may not be eligible for BCT and may require mastectomy, reiterating the necessity of NST in this subgroup. Lobular carcinomas typically have a poor response to chemotherapy when compared with ductal carcinomas. Mathieu and colleagues [16] reported the poor chemosensitivity is secondary to the immunohistochemical profile, making them unacceptable BCT candidates following neoadjuvant

chemotherapy. Most lobular carcinomas are strongly estrogen receptor/progesterone receptor (ER/PR) positive, and neoadjuvant endocrine therapy has been described to be more effective in these patients than chemotherapy. Dixon and colleagues [17] evaluated 40 patients with infiltrating lobular carcinoma who were not considered BCT candidates and treated them with 3 months of neoadjuvant letrozole. They report the rate of successful BCT in 81% of patients following neoadjuvant endocrine therapy.

The ability to undergo adjuvant radiation is an important consideration for women undergoing BCT. NSABP-B06 randomized 1851 women to total mastectomy, BCT, or BCT followed by radiation therapy. Patients who received BCT and adjuvant radiation had an loco-regional response of 14.3% versus 39.2% in women undergoing BCT without radiation [18]. There are few contraindications to adjuvant radiation, but include prior breast/chest radiation, pregnancy, and shoulder mobility (patients must be able to lie flat with the arm abducted). Relative contraindications include scleroderma and systemic lupus erythematosus. Because of the significant reduction in LRR, patients who cannot tolerate radiation or who have limited access to radiation facilities are poor candidates for BCT.

Becoming candidates for BCT and actually attempting/achieving tumor-free surgical margins has not been rigorously investigated. In both CALGB 40601 (human epidermal growth factor receptor-2^+, $HER2^+$) [19] and CALGB 40603 (triple-negative breast cancer, TNBC) [20], the treating surgeons were asked to assess whether a patient was a BCT candidate before and after NST. In CALGB 40601, 43% of patients converted from BCT ineligible to BCT eligible. When BCT was actually attempted, tumor-free surgical margins were achieved 80% of the time. Similarly, in CALGB 40603 (TNBC) [20], 42% of patients converted from BCT ineligible to BCT eligible. When BCT was attempted, tumor-free surgical margins were achieved in 93% of patients. Clearly, more research is necessary to determine which patients have truly been converted from BCT ineligible to BCT eligible with NST, but these 2 trials demonstrate that BCT can successfully be achieved in patients who get a good radiographic response to NST.

As the pCR rate to NST increases, omitting surgical resection of the primary breast cancer becomes a provocative, intellectual question. Does a woman with a pCR benefit from a partial mastectomy of the primary site? Several groups [21] have investigated the predictive value of a core biopsy or vacuum-assisted core biopsy (VACB) to determine pCR. Collectively, it appears VACB has a better negative-predictive value, much lower false-negative rate (FNR; <5%) than a core biopsy in patients with a radiographic complete response. A current national, clinical trial NRG BR005 (NCT03188393) is evaluating the negative-predictive value and FNR of performing VACB of primary breast site followed by standard of care partial mastectomy to evaluate if patients with a radiologic complete response may eventually be able to avoid surgical resection. The trial is currently accruing, and it is slated to close in the first quarter of 2019.

Neoadjuvant systemic therapy and the management of the axilla

Despite the first prospective, randomized NST trial, NSABP B-18, being published 30 years ago, the management of the axilla in these patients remains highly controversial. Historically, the traditional management of the axilla in these patients has been an axillary lymph node dissection (ALND). However, NST has been shown to have a significant role in reducing the axillary disease burden in patients with breast cancer with nodal involvement [22]. Thus, the timing and the method for nodal staging in patients planned for NST have been subjects of much debate. Two national, prospective NST trials demonstrate the management of the axillae in these patients is very heterogeneous [23]. In this section, a balanced discussion of the issues will be presented, trying to focus on prospective trial results, not single-institution treatment algorithms or biases.

The accurate assessment of the axillary lymph nodes for regional nodal metastases plays a crucial role in determining the extent of the disease before the use of NST. Given the low sensitivity of physical examination alone for detecting nodal metastases, it is important to evaluate the axilla accurately with noninvasive or minimally invasive approaches, before NST. Of the various imaging modalities (ultrasound, US, MRI, PET), axillary ultrasound (AUS) [15] has been widely adopted because of efficiency, reliability, and relative simplicity of the procedure. AUS can identify radiologically abnormal/enlarged lymph nodes, and then a US-guided fine-needle aspiration or core-needle biopsy can be performed.

For patients who present with clinically and radiographically negative axilla (cN0), performing a sentinel node (SN) biopsy before NST allows for accurate nodal staging negating any potential chemotherapy downstaging of the axillary nodes. Three large trials evaluated the SN identification rate and FNR to determine the feasibility of performing SN after NST. The first SENTINA (SENTinel NeoAdjuvant) study [24] was a European prospective multicenter study between 2009 and 2012 randomizing 1737 patients undergoing NST to the 4 following arms:

A. cN0 had upfront (-NST) SN that was pN0.
B. cN0 had upfront SN that was pN1, then post-NST SN + ALND.
C. cN1 or cN2 went to NST, and if converted to ycN0, had SN + ALND.
D. cN1 or cN2 went to NST and remained ycN1, had ALND only.

Comparing patients with cNO (arm A) with patients who converted to ycN0 (arm C), the investigators demonstrated a successful SN identification rate of 99.1% in patients cN0 (arm A) as compared with an 80.1% identification rate in patients who were ycN0 (Arm C). For the ycN0 group, the FNR was 24.3% if only 1 LN was removed, 18.5% if 2 LN were removed. In arm B, for patients undergoing a second SN, the identification rate was only 60.8% and FNR was 51.6%. The data strongly suggests SN biopsy is most accurate before NST. The disadvantage to this approach is the potential loss of opportunity to spare an ALND, especially in patients who actually achieve a pCR in the axillary nodes.

Performing an SN biopsy after NST provides a chance for nodal downstaging from the NST. If a patient converts from node positive to node negative, she could potentially be spared the added morbidity of ALND. A post hoc analysis of NSABP B-27 (described in detail earlier in the article) demonstrated SN biopsy after NST to be fairly successful, with an identification rate of 85% and a FNR of 9% [25]. Building on the findings of NSAPB B-27, the American College of Surgeons Oncology Group (ACOSOG) 1071 [26] carried out a prospective, phase 2 trial between 2009 and 2011 designed to evaluate the FNR of SN biopsy after NST in women with pathologically positive axillae. The trial evaluated 701 women with pathologic axillary nodes N1–N2 proven by fine-needle aspirate or core biopsy. All patients underwent SN biopsy followed by ALND. The FNR for a patient with cN1 disease was 12.6%, which was higher than the prespecified threshold of 10%. A post hoc subset analysis suggests that the FNR may be lowered by removing more than 2 SN, and by using dual-agent mapping.

The SN FNAC (Sentinel Node biopsy Following NeoAdjuvant Chemotherapy) [27] was a Canadian prospective multicenter trial from 2009 to 2012 with a similar design to ACOSOG 1071. This trial was a smaller patient cohort with 153 patients accrued. The FNR threshold was 10%, which was similar in other trials. They found that the SN identification rate after NST in cN1–2 was 87.6% and FNR was 8.4% when ypN0(i+) was considered a positive node. If ypN0(i+) was considered a negative node, the FNR increased to 13.3%.

Immunostains are not recommended to be routinely performed on SNs, except for patients with invasive lobular cancer [28]. Thus, collectively, all 3 trials demonstrate a FNR exceeding 10% when performing SN *after* NST. Investigators are continuing to look for ways to spare patients an unnecessary axillary dissection.

Post hoc analysis of ACOSOG 1071 suggested that removal of the axillary node, which had been biopsied and clipped, may be more accurate than an SN biopsy. Building on this finding, Caudle and colleagues [29] performed a prospective, single-institution trial evaluating if selective removal of the previous biopsy-proven positive clipped node, targeted axillary dissection (TAD) in addition to SN more accurately reflected the status of the remaining axillary nodes. They found that the previous clipped node was not removed during the SN biopsy in 23% of patients, and SN biopsy alone had a FNR of 10.1%. By identifying and removing the clipped node in addition to SN, the FNR was reduced to 2%. Although promising, TAD still needs to be replicated in other centers, and a prospective, multi-institutional trial is warranted. Clearly, more research/data are necessary so that women who do have a pCR in axillary nodes can be spared the morbidity of an ALND. The tumor status of the axilla after NST is a critical piece of prognostic information, and diagnostic accuracy is paramount.

Response to neoadjuvant systemic therapy as a prognostic indicator

The direct observation of the clinical and pathologic response to NST provides important information about the tumor biology and prognosis and further

guides treatment planning. The assessment of response to NST portends the ability to modify treatment approach based on initial response, which may be particularly important for early identification of nonresponsive tumors. Earlier studies suggested pCR as a surrogate for long-term outcomes, such as DFS, event-free survival (EFS), and OS [13,30]. It has been shown that patients who achieve a pCR have the greatest survival advantage, albeit the proportion of patients achieving a pCR is low [13,31]. However, the definition of pCR and its role in long-term outcomes varied significantly between the earlier trials, making the applicability of these findings to clinical practice challenging. To conclusively evaluate the evidence for the correlation between response to NST and long-term outcomes, the Food and Drug Administration established an international working group known as Collaborative Trials in Neoadjuvant Breast Cancer that conducted a pooled meta-analysis of the eligible clinical trials for neoadjuvant therapy [32]. The results of the analysis demonstrated a longer EFS and OS in patients with a pCR than in those with residual invasive cancer, establishing unequivocally the response to NST as a powerful individualized prognostic factor (Fig. 1). The study also showed a higher frequency of pCR in those with aggressive tumor biology (eg, hormone receptor-negative [HR^-] disease) than those with low-grade HR-positive disease reiterating the particular importance of NST in more aggressive disease subtypes.

PATIENT AND DRUG REGIMEN SELECTION FOR NEOADJUVANT SYSTEMIC THERAPY

The extent and type of NST recommended for an individual patient depend on the cancer biology, factors such as stage, grade, expression of ER and PR, and HER2 status. Although NST does not improve OS and DFS when compared with adjuvant therapy, it is an attractive approach to enhance surgical options and increase breast conservation [5,6]. The International Consensus Expert

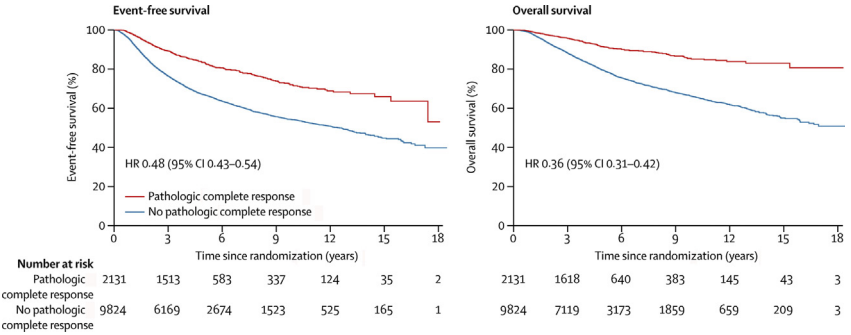

Fig. 1. Association of EFS and OS with pathologic complete response. CI, confidence interval; HR, hazard ratio. (*From* Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: The CTNeoBC pooled analysis. The Lancet. 2014;384(9938):166; with permission.)

Panel currently recommends consideration of NST for any patient in whom adjuvant chemotherapy is indicated [6]. However, the decision to choose NST over adjuvant approach requires a careful consideration of individual patient factors and preferences. The following reviews NST regimens by phenotype, including cytotoxic, targeted therapy, and neoadjuvant endocrine regimens.

Breast cancer is a clinically, histologically, and transcriptionally heterogeneous disease with prognostically significant subtypes. Certain subtypes have a better pathologic response to NST, reflecting a greater potential for curative intent even in some of the most aggressive phenotypes of breast cancer. Multiple, large randomized trials in the last decade have focused on characterizing the pathologic response of different subtypes with multiple preoperative chemotherapeutic agents (Table 1). The findings of the recent GeparQuinto, GBG-44 trial by Untch and colleagues [33] demonstrate substantially higher rates of pCR in Luminal-B/HER2-negative, HER2-positive nonluminal and TNBC with trastuzumab and chemotherapy combination. However, this response was not observed in the Luminal A and Luminal-B/HER2-positive patients. Similarly, the GeparSixto, GB-6 study showed a significant increase in the proportion of TNBC patients depicting pCR with the addition of carboplatin to the regime of neoadjuvant taxane, an anthracycline and targeted therapy reflecting the importance of molecular characterization of the tumor before selecting preoperative chemotherapeutic agents [34] (see Table 1).

Human epidermal growth factor receptor-2 overexpressing patients

For the HER2 overexpressing phenotype, several prospective, randomized clinical trials have been performed examining single-agent versus dual-agent HER2-directed therapy. In the NeoALTTO trial [35], NST paclitaxel was given with either single-agent HER2-directed therapy trastuzumab or lapatinib (a tyrosine kinase inhibitor) or both HER2-directed agents. It demonstrated a statistically higher pCR rate ($P = .0001$) in patients who received both agents (51.3%) as compared with single agents (24.7%, 29.5%). With a median follow-up of 3.8 years, there was no OS or DFS among the 3 groups, but the OS and DFS were significantly better in those who achieved pCR than those who not achieve pCR [36] (Table 2). Cancer and Leukemia Group B (CALGB) 40601 had a similar trial design with NST paclitaxel given with either single-agent (trastuzumab or lapatinib) or both HER2-directed therapies, but different findings. The single-agent lapatinib arm was closed early. The pCR in the dual-agent arm was higher (56%) versus single agent (46%), but this was not statistically significant ($P = .13$). Dual HER2-agent blockade with lapatinib does not seem to be the answer, but other HER2-directed agents have been investigated.

In the NeoSphere trial [37], the addition of pertuzumab (monoclonal antibody against the dimerization domain of HER2) to trastuzumab with or without T showed a dramatic increase in the rates of pCR (45.8%) as compared with single-agent HER2-directed therapy (29%, 24%) [37,38]. Five-year progression-free survival is the highest in the dual-agent HER2-directed therapy

Table 1
Important randomized clinical trials evaluating various chemotherapeutic drugs/regimens

Trial	Number of patients enrolled (n)	Neoadjuvant regimen evaluated	Median follow-up (mo)	Results/conclusions
Buzdar et al, [24] 2007	42	Paclitaxel + 4 cycles of FEC with OR without trastuzumab	36	• pCR rate substantially higher in patients treated with chemotherapy plus trastuzumab vs chemotherapy alone (66.7% vs 25%)
NeoALTTO Trial (2008–2010) (NCT00553358) [25]	455	Trastuzumab/lapatinib/ trastuzumab + lapatinib with paclitaxel followed by adjuvant FEC + same anti-HER2 therapy (all $HER2^+$ tumors)	45	• Proportion of patients achieving pCR significantly higher in combination group (51.3%) vs trastuzumab alone (29.5%) • No difference in DFS or OS among groups
GeparTrio Trial (2002–2005) [26]	2072	Two cycles of TAC followed by 4/6 cycles of TAC in early responders	62	• DFS and OS longer in TAC × 8 cycles group • DFS and OS longer in HR^+ tumors after response guided NST
GeparQuattro Trial (2006–2009) [27] (NCT00288002)	1509	Four cycles of EC followed by 4 cycles of T (EC-T)/T plus capcetabine (EC-TX)/T followed by capcetabine (EX-T-X) (with trastuzumab for $HER2^+$ tumors)	65	• Trastuzumab with anthracycline-taxane–based chemotherapy significantly higher pCR than reference group (31.7% vs 15.7%) • No difference in DFS and OS among $HER2^+$ and $HER2^-$ cohorts • OS after progression better in $HER2^+$ patients treated with anti-HER2 vs $HER2^-$ treated with chemotherapy alone

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Table 1 (*continued*)

Trial	Number of patients enrolled (n)	Neoadjuvant regimen evaluated	Median follow-up (mo)	Results/conclusions
NOAH Trial (Neoadjuvant Herceptin in Patients With HER2-Positive Locally Advanced Breast Cancer) [28]	235	Trastuzumab plus anthracycline-taxane–based chemotherapy/ chemotherapy alone (All $HER2^+$ tumors)	65	• pCR rate in trastuzumab group higher (38%) vs chemotherapy-only group (19%) • Significant association between pCR and OS, DFS • EFS significantly higher (58%) in trastuzumab group at 5.4 y vs chemotherapy-only group (43%)
NeoSphere Trial [29]	417	Trastuzumab + T/ trastuzumab + pertuzumab + T/ trastuzumab + pertuzumab/ pertuzumab + T with 3 cycles of FEC in all groups	60	• Highest 5-y PFS in group receiving trastuzumab + pertuzumab + T (86%) • Highest 5-y DFS in group receiving trastuzumab + pertuzumab + T (84%)
GeparQuinto Trial [30] (NCT00567554)	1948	Epirubicin + cyclophosphamide + T with OR without bevacizumab	NA	• Significantly higher rates of pCR in triple-negative patients with added bevacizumab (39.3% vs 27.9%) • No significant difference in pCR rates with addition of bevacizumab to HR+ patients

Abbreviations: FEC, fluorouracil, epirubicin, cyclophosphamide; NA, not applicable; PFS, progression-free survival; TAC, T, doxorubicin, cyclophosphamide.

Table 2
Recent/ongoing clinical trials evaluating HER2 over expressing tumors

Trial	Number of patients (n)	Regimen/agent	Preliminary findings
CALGB 40601 [40]	305	Paclitaxel + trastuzumab OR paclitaxel + trastuzumab + lapatinib	• No significant differences in pCR rates with or without addition of lapatinib • Toxicity rates were significantly higher on lapatinib arm
EMILIA Trial [37] (NCT00829166)	991	Trastuzumab emtansine (T-DM1) vs capecitabine + lapatinib	• Significantly prolonged PFS and OS and less toxicity with T-DM1 than capecitabine + lapatinib
MARIANNE Study [38]	1095	Trastuzumab emtansine (T-DM1) + pertuzumab vs trastuzumab + taxane vs T-DM1 alone	• T-DM1 and T-DM1 plus pertuzumab showed noninferior PFS with better tolerability than trastuzumab + taxane
ADAPT trial [39][a]	134	Trastuzumab + pertuzumab with (T+P+Pac) OR without paclitaxel (T+P)	• pCR rate substantially higher in T+P+Pac arm (89.2% vs 36.3%)
KRISTINE (or TRIO-021) [40][b] (NCT02131064)	444	T + carboplatin with trastuzumab + pertuzumab (TCHP) vs T-DM1 + pertuzumab (KP)	• pCR rates higher in the TCHP group than in KP group (55.7% vs 44.4%) • More women in the TCHP group underwent breast conserving surgery than in KP group (52.6% vs 41.7%)

Neoadjuvant and Personalized Adaptive Novel Agents to Treat Breast Cancer.
[a]Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early Breast Cancer.
[b]A Study Comparing Kadcyla Plus Perjeta Treatment to Chemotherapy Combined With Herceptin Plus Perjeta in Patients With HER2-Positive Breast Cancer; NCT02131064.

[39]. Similarly, the KRISTINE trial [38] randomized patients to trastuzumab emtansine and pertuzumab versus T, carboplatin, trastuzumab, and pertuzumab with the primary endpoint pCR. The trastuzumab plus pertuzumab arm had the higher pCR rate (55.7% vs 44.4%, $P = .016$).

Collectively, these HER2 NST trials suggest the highest pCR rate is seen when trastuzumab and pertuzumab are combined with chemotherapy. It remains to be seen whether this improved pCR rate translates into an improved OS and DFS (see Table 2).

Triple-negative patients

TNBC, characterized by the lack of ER, PR, and HER2, has no currently available targeted agents. The standard NST regimen remains polychemotherapy. Approximately one-third of TNBC patients will achieve a pCR to NST with anthracycline and taxane [41].

TNBC, currently the most aggressive form of breast cancer, has long evaded targeted therapy. In GeparSixto [34], the TNBC patients were randomized to polychemotherapy ± carboplatin. The addition of carboplatin significantly increased the pCR rate (53.2% vs 36.9%, $P = .005$). CALGB 40603 (ALLIANCE) [42] performed a randomized phase 2 NST trial to evaluate this impact of carboplatin and/or bevacizumab to standard polychemotherapy. The addition of carboplatin significantly increased the pCR rate breast/axilla (54% vs 41%, $P = .0029$). Recent results from the CALGB 40603 and the GeparSixto trials show significantly improved pCR rates with the addition of neoadjuvant carboplatin [34,42]. Including the results of another polychemotherapy ± bevacizumab (BEATRICE), the addition of neoadjuvant bevacizumab does not improve the proportion of patients achieving pCR and may increase the likelihood of adverse events [42–44]. Despite these encouraging results, whether this improvement in pCR rates translates into improved OS and DFS for patients remains questionable. This yet unproven correlation highlights the need for careful selection of chemotherapeutic agents based on the patient's tumor characteristics and utilization of established evidence for subtype specific therapy (Table 3).

Hormone receptor–positive, human epidermal growth factor receptor-2 –negative patients

The patients with $HR^+/HER2^-$ disease, also classified as luminal subtype A or B on gene-expression profiling, are usually slow-growing, low-grade tumors with a good overall prognosis [47]. However, the rate of pCR to NST in $HR^+/HER2^-$ patients is strikingly low, with pCR rates varying from 2% to 10% [6,48]. Significantly improved response rates are observed with the use of neoadjuvant endocrine therapy in this tumor subtype (fully discussed later in this article). Whether there is a benefit of concurrent administration of neoadjuvant cytotoxic chemotherapy and endocrine therapy remains questionable. Some data suggest a benefit of combination letrozole and cyclophosphamide over letrozole alone (response rate of 89.2% vs 72.8%) in elderly HR^+ patients [49] A randomized phase 2 clinical trial conducted by Sugiu and colleagues [45]

Table 3
Therapeutic regimens evaluated/under evaluation for triple-negative breast cancer

Trial	Number of patients (n)	Regimen/agent	Results/conclusions
CALGB 40603 Trial Impact of the Addition of Carboplatin and/or Bevacizumab to Neoadjuvant Once-per-Week Paclitaxel Followed by Dose-Dense Doxorubicin and Cyclophosphamide on Pathologic Complete Response Rates in Stage II to III Triple-Negative Breast Cancer [36]	443	Paclitaxel followed by doxorubicin + cyclophosphamide with OR without cisplatin and/or bevacizumab	• Addition of carboplatin significantly increased the pCR rates as compared with those did not receive carboplatin (60% vs 46%) • Addition of bevacizumab significantly increased the pCR rates as compared with those did not receive carboplatin (59% vs 48%) • Patients receiving both carboplatin and bevacizumab had a pCR of 67%
GeparSixto GBG 66 [31] (NCT01426880)	588	Paclitaxel + doxorubicin + trastuzumab ($HER2^+$ tumors only) + bevacizumab (triple negative tumors only) with OR without carboplatin	• Significant increase in pCR rates in triple-negative disease with addition of carboplatin (53.2% vs 36.9%) • No benefit observed in terms of pCR in $HER2^+$ tumors with addition of carboplatin (32.8% vs 36.8%)
BEATRICE Trial Adjuvant bevacizumab-containing therapy in triple-negative breast cancer [45] (NCT00528567)	2591	Anthracycline and/or taxane with OR without bevacizumab	• No difference in 3-y DFS in patients receiving bevacizumab than those who did not (83.7% vs 82.7%)
Eastern Cooperative Oncology Group E5103 Trial [46]	4994	Doxorubicin + cyclophosphamide followed by paclitaxel alone OR with concurrent bevacizumab OR with sequential bevacizumab	• No difference in 4-y DFS or OS with addition of bevacizumab to standard chemotherapy

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Table 3
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Trial	Number of patients (n)	Regimen/agent	Results/conclusions
A Co-Clinical Trial in Triple Negative Breast Cancer Patients with Genoproteomic Discovery (NCT02124902)	70 (anticipated)	T + carboplatin	Anticipated completion June 2018 Primary outcome of interest: –pCR rates
A Randomized, Double-Blind, Phase III Clinical Trial of Neoadjuvant Chemotherapy With Atezolizumab or Placebo in Patients With Triple-Negative Breast Cancer Followed by Adjuvant Continuation of Atezolizumab or Placebo (NCT03281954)	1520 (anticipated)	Paclitaxel + carboplatin, followed by doxorubicin/epirubicin and cyclophosphamide with OR without atezolizumab	Anticipated completion June 2024 Primary outcome of interest: pCR rates and EFS
CADENCE: Carboplatin and Docetaxel in Neoadjuvant Treatment of ER-Negative, HER2-Negative Breast Cancer: A Co-Clinical Trial with Genoproteomic Discovery (NCT02547987)	44 (anticipated)	T + carboplatin	Anticipated completion September 2020

A Phase II Randomized Controlled Trial of Genomically Directed Therapy After Preoperative Chemotherapy in Patients With Triple Negative Breast Cancer: Hoosier Oncology Group BRE12-158 (NCT02101385)	136 (anticipated)	Experimental Arm A (genomically directed monotherapy) or Control Arm B (standard therapy) Actionable pathways/agents • PIK3CA, PTEN: Everolimus • TOP2A: Doxorubicin • PARP1, BRCA1: Cisplatin and olaparib • VEGFA: Bevacizumab • TYMP: Capecitabine • SSTR2: Octreotide • MGMT: Temozolomide • MYC: Paclitaxel • EGFR: Cetuximab • COX2: Celecoxib • hENT: Gemcitabine • MET: Crizotinib	Anticipated completion December 2021 Primary outcome of interest: Impact of genomic characterization of tumor and effect on disease progression/treatment response by targeted therapy
A Randomized, Double-Blind, Phase III Clinical Trial of Neoadjuvant Chemotherapy With Atezolizumab or Placebo in Patients With Triple-Negative Breast Cancer Followed by Adjuvant Continuation of Atezolizumab or Placebo (NCT03281954)	1520	Paclitaxel + carboplatin, followed by doxorubicin/epirubicin and cyclophosphamide with OR without atezolizumab	Anticipated completion June 2024 Primary outcome of interest: pCR rates and EFS

showed no difference in pCR rates in HR^+ patients administered concurrent chemotherapy and endocrine therapy as compared with chemotherapy alone. However, the reduction in tumor size was significantly greater in the concurrent group. This conflicting body of evidence reflects the need of further studies to evaluate the role of concurrent endocrine and chemotherapy in the management of $HR^+/HER2^-$ patient population (Table 4).

Neoadjuvant endocrine therapy

Given the success of adjuvant antiestrogen therapy for patients who are ER^+, there has been a considerable interest in leveraging the effect of endocrine therapy directed against HRs in the neoadjuvant setting.

Neoadjuvant letrozole trial

In a double-blind phase 3 randomized trial, postmenopausal women with large ER^+ and/or PR^+ breast cancers who required mastectomy or were locally advanced and inoperable were randomized to receive letrozole or tamoxifen for 4 months as primary treatment [55]. Objective response rates by clinical examination and imaging favored the letrozole-treated patients (60% vs 41%; $P = .004$). There was a higher rate of breast-conserving surgery in the letrozole group (48%) than in the tamoxifen group (36%) ($P = .036$).

Neoadjuvant anastrozole trials

There have been 2 large randomized studies comparing anastrozole with tamoxifen in postmenopausal women with HR^+ breast cancer.

In the IMmediate Preoperative Arimidex, Tamoxifen or Combined with Tamoxifen (IMPACT) trial, patients were randomized to receive anastrozole or tamoxifen or both in combination for 3 months before surgery [56]. The primary end point was objective clinical response measured by calipers, with US measurement. There was no significant difference in objective response between the 3 treatments as measured by calipers and US. After 3 months, for patients initially assessed as requiring mastectomy, significantly more were deemed suitable for breast-conserving surgery in the anastrozole arm (46%) than tamoxifen arm (22%) ($P = .03$), but not all patients accepted this recommendation (actual BCT rates, $P =$ not significant).

In the PROACT (PReOperarive Arimidex Compared with Tamoxifen) trial [57], patients were randomized to receive either anastrozole or tamoxifen for 3 months. The primary end point was objective tumor response measured by US scan, and caliper measurement was a secondary end point. No significant difference in objective response was seen between treatment arms. There was, however, a significantly higher objective response in favor of anastrozole in those patients initially assessed as requiring mastectomy (36.6% vs 24.2% on US, $P = .03$; and 48.6% vs 35.8% with calipers, $P = .04$).

A combined analysis of these 2 studies compared ORR and surgery and failed to show any significant difference in objective response or breast-conserving rates between tamoxifen and anastrozole [58]. There was, however, a significant improvement in ORR in favor of anastrozole in the subgroup of

Table 4
Clinical trials evaluating neoadjuvant systemic therapy regimens for hormone receptor–positive breast cancer

Trial	Number of patients enrolled (n)	Neoadjuvant regimen evaluated	Results/conclusions
STAGE Trial [46] (NCT00605267)	204	Goserelin + anastrozole OR goserelin + tamoxifen	• Response rates higher in anastrozole group than those in the tamoxifen group (70.4% vs 50.5%)
Semiglazov et al, [50] 2007	121	Anastrozole/exemestane OR doxorubicin + paclitaxel	• No significant difference in clinical response/pCR rates between the endocrine arm and chemotherapy arm • Higher toxicity in the chemotherapy arm
METEOR Trial [51] (NCT01589367)	208 (anticipated)	Letrozole + metformin or letrozole + placebo	• *Currently ongoing* (primary outcome of interest: clinical response rate)
Baselga et al, [52] 2009 (NCT00107016)	270	Letrozole + everolimus OR letrozole + placebo	• Clinical response rate higher in combination arm than that in letrozole alone (68.1% vs 59.1%) • Reduction of Ki-67 levels occurred in a higher proportion of patients in the combination arm than letrozole alone (57% vs 30%)
GEICAM/2006–03 Trial [53]	95	Chemotherapy (CT) (epirubicin + cyclophosphamide + T) OR hormonotherapy (HT)(exemestane [+ goserelin in premenopausal patients])	• Overall higher clinical response rate in the CT arm than HT arm (66% vs 48%) • No significant difference between the 2 arms in patients with low Ki-67 levels (CT: 63%, HT: 58%) • Better response rates with CT in those with high Ki-67 levels than HT (67% vs 42%)
NEOCENT Trial [54] (NCT00963729)	44	CT (fluorouracil + epirubicin + cyclophosphamide followed by T) OR letrozole alone	• Highest 5-y PFS in group receiving trastuzumab + pertuzumab + T (86%) • Highest 5-y DFS in group receiving trastuzumab + pertuzumab + T (84%)

patients who were considered to require mastectomy or be inoperable at the outset (47% vs 35%; $P = .026$) and on US response (36% vs 26%; $P = .048$). Collectively, these data suggest anastrozole is superior to tamoxifen in patients' tumors that are large and require mastectomy or are inoperable or locally advanced at diagnosis.

The response to the endocrine agents has been shown to correlate with the level of ER expression. Among the endocrine therapy agents, aromatase inhibitors are more effective than tamoxifen in facilitating BCT, as shown by Eiermann and colleagues [55], and the IMPACT trial [56]. Subsequently, the ACOSOG Z1031 trial was a randomized phase 2 trial in 377 women with clinical stage II to II ER-positive breast cancer randomized to 1 of 3 commonly used AIs (letrozole, anastrozole, and exemestane) administered in the neoadjuvant setting [59]. The results of the trial demonstrated significantly improved surgical outcomes especially in patients with Luminal-A subtype of breast cancer. The rate of conversion to BCT was similar among all 3 agents; however, the suppression of circulating estradiol was observed to be highest in patients taking letrozole. Currently, 2 large prospective trials are underway to assess the effect of endocrine therapy agents in the neoadjuvant setting on long-term clinical outcomes (ALTERNATE Trial, NCT01953588; FACE Trial, NCT00248170).

SUMMARY

NST remains the cornerstone for management of large inoperable breast tumors and for inflammatory breast cancer. The use of NST in patients with operable breast cancer has increased substantially the last 2 decades leading to increased BCT rates with equivalent OS and DFS when compared with patients treated with adjuvant therapy. The drastic improvements in the understanding of the tumor biology and recent advances in molecular analysis have facilitated rapid, accurate, molecular subtyping of the tumor and development of efficacious targeted systemic agents, particularly in HER2 overexpressing patients. The pCR rate has increased, but corresponding OS has not yet increased. The challenge remains to translate this wealth of knowledge to the clinic, facilitating the use of NST tailored to the molecular signature of the individual patient.

References

[1] Sorace RA, Bagley CS, Lichter AS, et al. The management of nonmetastatic locally advanced breast cancer using primary induction chemotherapy with hormonal synchronization followed by radiation therapy with or without debulking surgery. World J Surg 1985;9(5):775–85.

[2] Perloff M, Lesnick GJ. Chemotherapy before and after mastectomy in stage III breast cancer. Arch Surg 1982;117(7):879–81.

[3] Schick P, Goodstein J, Moor J, et al. Preoperative chemotherapy followed by mastectomy for locally advanced breast cancer. J Surg Oncol 1983;22(4):278–82.

[4] Barry PA, Schiavon G. Primary systemic treatment in the management of operable breast cancer: best surgical approach for diagnosis, biological evaluation, and research. J Natl Cancer Inst Monogr 2015;2015(51):4–8.

[5] Mauri D, Pavlidis N, Ioannidis JP. Neoadjuvant versus adjuvant systemic treatment in breast cancer: a meta-analysis. J Natl Cancer Inst 2005;97(3):188–94.
[6] Kaufmann M, von Minckwitz G, Bear HD, et al. Recommendations from an international expert panel on the use of neoadjuvant (primary) systemic treatment of operable breast cancer: new perspectives 2006. Ann Oncol 2007;18(12):1927–34.
[7] Jacquillat C, Baillet F, Blondon J, et al. Preliminary results of "neoadjuvant" chemotherapy in initial management of breast cancer (BC). Proc ASCO 1983;2:112.
[8] Jacquillat CI, Weil M, Auclerc G, et al. Neoadjuvant chemotherapy in the conservative management of breast cancers: study of 143 patients. Recent Results Cancer Res 1986;103: 113–9.
[9] Fisher B, Bryant J, Wolmark N, et al. Effect of preoperative chemotherapy on the outcome of women with operable breast cancer. J Clin Oncol 1998;16(8):2672–85.
[10] Wolmark N, Wang J, Mamounas E, et al. Preoperative chemotherapy in patients with operable breast cancer: nine-year results from National Surgical Adjuvant Breast and Bowel Project B-18. J Natl Cancer Inst Monogr 2001;(30):96–102.
[11] van der Hage JA, van de Velde CJ, Julien JP, et al. Preoperative chemotherapy in primary operable breast cancer: results from the European Organization for Research and Treatment of Cancer trial 10902. J Clin Oncol 2001;19(22):4224–37.
[12] van Nes JG, Putter H, Julien JP, et al. Preoperative chemotherapy is safe in early breast cancer, even after 10 years of follow-up; clinical and translational results from the EORTC trial 10902. Breast Cancer Res Treat 2009;115(1):101–13.
[13] Rastogi P, Anderson SJ, Bear HD, et al. Preoperative chemotherapy: updates of National Surgical Adjuvant Breast and Bowel Project Protocols B-18 and B-27. J Clin Oncol 2008;26(5):778–85.
[14] Newman LA, Buzdar AU, Singletary SE, et al. A prospective trial of preoperative chemotherapy in resectable breast cancer: predictors of breast-conservation therapy feasibility. Ann Surg Oncol 2002;9(3):228–34.
[15] Henry-Tillman R, Glover-Collins K, Preston M, et al. The SAVE review: sonographic analysis versus excision for axillary staging in breast cancer. J Am Coll Surg 2015;220(4):560–7.
[16] Mathieu MC, Rouzier R, Llombart-Cussac A, et al. The poor responsiveness of infiltrating lobular breast carcinomas to neoadjuvant chemotherapy can be explained by their biological profile. Eur J Cancer 2004;40(3):342–51.
[17] Dixon JM, Mamman U, Thomas J. Accuracy of intraoperative frozen-section analysis of axillary nodes. Edinburgh Breast Unit team. Br J Surg 1999;86(3):392–5.
[18] Fisher B, Anderson S, Bryant J, et al. Twenty-year follow-up of a randomized trial comparing total mastectomy, lumpectomy, and lumpectomy plus irradiation for the treatment of invasive breast cancer. N Engl J Med 2002;347(16):1233–41.
[19] Golshan M, Cirrincione CT, Sikov WM, et al. Impact of neoadjuvant therapy on eligibility for and frequency of breast conservation in stage II-III HER2-positive breast cancer: surgical results of CALGB 40601 (Alliance). Breast Cancer Res Treat 2016;160(2):297–304.
[20] Golshan M, Cirrincione CT, Sikov WM, et al. Impact of neoadjuvant chemotherapy in stage II-III triple negative breast cancer on eligibility for breast-conserving surgery and breast conservation rates: surgical results from CALGB 40603 (Alliance). Ann Surg 2015;262(3): 434–9 [discussion: 438–9].
[21] Kuerer HM, Vrancken Peeters M, Rea DW, et al. Nonoperative management for invasive breast cancer after neoadjuvant systemic therapy: conceptual basis and fundamental international feasibility clinical trials. Ann Surg Oncol 2017;24(10):2855–62.
[22] Kuerer HM, Sahin AA, Hunt KK, et al. Incidence and impact of documented eradication of breast cancer axillary lymph node metastases before surgery in patients treated with neoadjuvant chemotherapy. Ann Surg 1999;230(1):72–8.
[23] Ollila DW, Cirrincione CT, Berry DA, et al. Axillary management of stage II/III breast cancer in patients treated with neoadjuvant systemic therapy: results of CALGB 40601 (HER2-positive) and CALGB 40603 (triple-negative). J Am Coll Surg 2017;224(4):688–94.

[24] Kuehn T, Bauerfeind I, Fehm T, et al. Sentinel-lymph-node biopsy in patients with breast cancer before and after neoadjuvant chemotherapy (SENTINA): a prospective, multicentre cohort study. Lancet Oncol 2013;14(7):609–18.
[25] Mamounas EP, Brown A, Anderson S, et al. Sentinel node biopsy after neoadjuvant chemotherapy in breast cancer: results from National Surgical Adjuvant Breast and Bowel Project Protocol B-27. J Clin Oncol 2005;23(12):2694–702.
[26] Boughey JC, Suman VJ, Mittendorf EA, et al. Sentinel lymph node surgery after neoadjuvant chemotherapy in patients with node-positive breast cancer: the ACOSOG Z1071 (Alliance) clinical trial. JAMA 2013;310(14):1455–61.
[27] Boileau JF, Poirier B, Basik M, et al. Sentinel node biopsy after neoadjuvant chemotherapy in biopsy-proven node-positive breast cancer: the SN FNAC study. J Clin Oncol 2015;33(3):258–64.
[28] Patel A, D'Alfonso T, Cheng E, et al. Sentinel lymph nodes in classic invasive lobular carcinoma of the breast: cytokeratin immunostain ensures detection, and precise determination of extent, of involvement. Am J Surg Pathol 2017;41(11):1499–505.
[29] Caudle AS, Yang WT, Krishnamurthy S, et al. Improved axillary evaluation following neoadjuvant therapy for patients with node-positive breast cancer using selective evaluation of clipped nodes: implementation of targeted axillary dissection. J Clin Oncol 2016;34(10):1072–8.
[30] Smith IC, Heys SD, Hutcheon AW, et al. Neoadjuvant chemotherapy in breast cancer: significantly enhanced response with docetaxel. J Clin Oncol 2002;20(6):1456–66.
[31] Eltahir A, Heys SD, Hutcheon AW, et al. Treatment of large and locally advanced breast cancers using neoadjuvant chemotherapy. Am J Surg 1998;175(2):127–32.
[32] Cortazar P, Zhang L, Untch M, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. Lancet 2014;384(9938):164–72.
[33] Untch M, Loibl S, Bischoff J, et al. Lapatinib versus trastuzumab in combination with neoadjuvant anthracycline-taxane-based chemotherapy (GeparQuinto, GBG 44): a randomised phase 3 trial. Lancet Oncol 2012;13(2):135–44.
[34] von Minckwitz G, Schneeweiss A, Loibl S, et al. Neoadjuvant carboplatin in patients with triple-negative and HER2-positive early breast cancer (GeparSixto; GBG 66): a randomised phase 2 trial. Lancet Oncol 2014;15(7):747–56.
[35] Baselga J, Bradbury I, Eidtmann H, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): a randomised, open-label, multicentre, phase 3 trial. Lancet 2012;379(9816):633–40.
[36] de Azambuja E, Holmes AP, Piccart-Gebhart M, et al. Lapatinib with trastuzumab for HER2-positive early breast cancer (NeoALTTO): survival outcomes of a randomised, open-label, multicentre, phase 3 trial and their association with pathological complete response. Lancet Oncol 2014;15(10):1137–46.
[37] Gianni L, Pienkowski T, Im YH, et al. Efficacy and safety of neoadjuvant pertuzumab and trastuzumab in women with locally advanced, inflammatory, or early HER2-positive breast cancer (NeoSphere): a randomised multicentre, open-label, phase 2 trial. Lancet Oncol 2012;13(1):25–32.
[38] Hurvitz SA, Martin M, Symmans WF, et al. Neoadjuvant trastuzumab, pertuzumab, and chemotherapy versus trastuzumab emtansine plus pertuzumab in patients with HER2-positive breast cancer (KRISTINE): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2018;19(1):115–26.
[39] Gianni L, Pienkowski T, Im YH, et al. 5-year analysis of neoadjuvant pertuzumab and trastuzumab in patients with locally advanced, inflammatory, or early-stage HER2-positive breast cancer (NeoSphere): a multicentre, open-label, phase 2 randomised trial. Lancet Oncol 2016;17(6):791–800.
[40] Carey LA, Berry DA, Ollila DW, et al. Clinical and translational results of CALGB 40601: a neoadjuvant phase III trial of weekly paclitaxel and trastuzumab with or without lapatinib for

HER2-positive breast cancer. Journal of the Proceedings of the American Society of Clinical Oncology 2013;31:500, (abstr).
[41] Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. J Clin Oncol 2008;26(8):1275–81.
[42] Sikov WM, Berry DA, Perou CM, et al. Impact of the addition of carboplatin and/or bevacizumab to neoadjuvant once-per-week paclitaxel followed by dose-dense doxorubicin and cyclophosphamide on pathologic complete response rates in stage II to III triple-negative breast cancer: CALGB 40603 (Alliance). J Clin Oncol 2015;33(1):13–21.
[43] Cameron D, Brown J, Dent R, et al. Adjuvant bevacizumab-containing therapy in triple-negative breast cancer (BEATRICE): primary results of a randomised, phase 3 trial. Lancet Oncol 2013;14(10):933–42.
[44] Miller K, O'Neill AM, Dang CT, et al. Bevacizumab (Bv) in the adjuvant treatment of HER2-negative breast cancer: final results from Eastern Cooperative Oncology Group E5103. J Clin Oncol 2014;32(15_suppl):500.
[45] Sugiu K, Iwamoto T, Kelly CM, et al. Neoadjuvant chemotherapy with or without concurrent hormone therapy in estrogen receptor-positive breast cancer: NACED-randomized multicenter phase II trial. Acta Med Okayama 2015;69(5):291–9.
[46] Masuda N, Sagara Y, Kinoshita T, et al. Neoadjuvant anastrozole versus tamoxifen in patients receiving goserelin for premenopausal breast cancer (STAGE): a double-blind, randomised phase 3 trial. Lancet Oncol 2012;13(4):345–52.
[47] Sorlie T, Perou CM, Tibshirani R, et al. Gene expression patterns of breast carcinomas distinguish tumor subclasses with clinical implications. Proc Natl Acad Sci U S A 2001;98(19):10869–74.
[48] Colleoni M, Viale G, Zahrieh D, et al. Chemotherapy is more effective in patients with breast cancer not expressing steroid hormone receptors: a study of preoperative treatment. Clin Cancer Res 2004;10(19):6622–8.
[49] Bottini A, Generali D, Brizzi MP, et al. Randomized phase II trial of letrozole and letrozole plus low-dose metronomic oral cyclophosphamide as primary systemic treatment in elderly breast cancer patients. J Clin Oncol 2006;24(22):3623–8.
[50] Semiglazov VF, Semiglazov VV, Dashyan GA, et al. Phase 2 randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with estrogen receptor-positive breast cancer. Cancer 2007;110(2):244–54.
[51] Kim J, Lim W, Kim EK, et al. Phase II randomized trial of neoadjuvant metformin plus letrozole versus placebo plus letrozole for estrogen receptor positive postmenopausal breast cancer (METEOR). BMC Cancer 2014;14:170.
[52] Baselga J, Semiglazov V, van Dam P, et al. Phase II randomized study of neoadjuvant everolimus plus letrozole compared with placebo plus letrozole in patients with estrogen receptor-positive breast cancer. J Clin Oncol 2009;27(16):2630–7.
[53] Alba E, Calvo L, Albanell J, et al. Chemotherapy (CT) and hormonotherapy (HT) as neoadjuvant treatment in luminal breast cancer patients: results from the GEICAM/2006-03, a multicenter, randomized, phase-II study. Ann Oncol 2012;23(12):3069–74.
[54] Palmieri C, Cleator S, Kilburn LS, et al. NEOCENT: a randomised feasibility and translational study comparing neoadjuvant endocrine therapy with chemotherapy in ER-rich postmenopausal primary breast cancer. Breast Cancer Res Treat 2014;148(3):581–90.
[55] Eiermann W, Paepke S, Appfelstaedt J, et al. Preoperative treatment of postmenopausal breast cancer patients with letrozole: a randomized double-blind multicenter study. Ann Oncol 2001;12(11):1527–32.
[56] Smith IE, Dowsett M, Ebbs SR, et al. Neoadjuvant treatment of postmenopausal breast cancer with anastrozole, tamoxifen, or both in combination: the Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen (IMPACT) multicenter double-blind randomized trial. J Clin Oncol 2005;23(22):5108–16.
[57] Cataliotti L, Buzdar AU, Noguchi S, et al. Comparison of anastrozole versus tamoxifen as preoperative therapy in postmenopausal women with hormone receptor-positive breast

cancer: the Pre-Operative "Arimidex" Compared to Tamoxifen (PROACT) trial. Cancer 2006;106(10):2095–103.

[58] Smith IE. Anastrozole versus tamoxifen as preoperative therapy for oestrogen receptor-positive breast cancer in postmenopausal women:combined analysis of the IMPACT and PROACT trials. 4th European Breast Cancer Conference. Hamburg, Germany, March 17, 2004.

[59] Ellis MJ, Suman VJ, Hoog J, et al. Randomized phase II neoadjuvant comparison between letrozole, anastrozole, and exemestane for postmenopausal women with estrogen receptor-rich stage 2 to 3 breast cancer: clinical and biomarker outcomes and predictive value of the baseline PAM50-based intrinsic subtype–ACOSOG Z1031. J Clin Oncol 2011;29(17):2342–9.