Current Oncology Reports (2022) 24:1779–1789
https://doi.org/10.1007/s11912-022-01331-y

BREAST CANCER (RA LEON FERRE, SECTION EDITOR)

Optimization of Neoadjuvant Therapy for Early-Stage Triple-Negative and HER2 + Breast Cancer

Sneha Phadke[1]

Accepted: 29 July 2022 / Published online: 1 October 2022

Abstract

Purpose of Review Neoadjuvant, or pre-operative, therapy for the treatment of early-stage breast cancer has several potential benefits, especially for patients with triple-negative or HER2 + subtypes. This review provides an overview of optimal practices for utilizing neoadjuvant therapy, guidelines for decision-making, and ongoing clinical trials that are expected to help refine therapy choices.

Recent Findings For triple-negative disease, the addition of the checkpoint inhibitor pembrolizumab to chemotherapy has shown remarkable efficacy, increasing response rates and survival. In the HER2 + setting, we are now able to safely avoid use of anthracyclines in most patients and refine adjuvant treatment choices based on response to neoadjuvant therapy.

Summary Results from recent clinical studies highlight advancements in systemic therapy and mark steps toward precision medicine, although reliable biomarkers of therapy response are still needed.

Keywords Breast cancer · Triple negative · HER2 · Neoadjuvant therapy

Introduction

While the incidence of breast cancer has been slowly rising, breast cancer mortality rates have dropped over the last few decades, primarily due to improvements in systemic therapy. Determining the optimal sequence of therapies requires a multidisciplinary approach. The stage, receptor status of the cancer, patient-related factors, and desired surgery all play a role in decision-making. In HER2 + and triple-negative subtypes, standard systemic therapy options consist of chemotherapy, targeted therapy, and checkpoint inhibitor (CPI) therapy, with ongoing clinical trials investigating novel agents and risk-adapted approaches to patient care.

This article is part of the Topical Collection on *Breast Cancer*

✉ Sneha Phadke
Sneha-Phadke@uiowa.edu

[1] Department of Internal Medicine, Holden Comprehensive Cancer Center, University of Iowa Carver College of Medicine, Iowa City, IA, USA

Background on Neoadjuvant Chemotherapy

It is important to note that there is no direct evidence suggesting a difference in breast cancer outcomes between administering chemotherapy in the neoadjuvant versus adjuvant setting [1, 2]. However, if a patient is given neoadjuvant therapy (NT), adjuvant systemic therapy may then be adapted to therapeutic response. Evaluating the response to NT is a critical decision-making juncture, considering the importance of the residual cancer burden (RCB) on prognosis. Tailoring therapy based on RCB may improve outcomes, particularly in human epidermal growth factor receptor-2 positive (HER2 +) and triple-negative breast cancer (TNBC) subtypes. In a large retrospective cohort study, the achievement of pathologic complete response (pCR) was associated with an excellent relapse-free survival (RFS) at 8 years in all breast cancer subtypes, with increasing RCB associated with an increasingly higher risk of relapse [3]. The RCB system has been validated in subsequent independent studies and is now a frequently used outcome measure in NT clinical trials [4–6]. One large meta-analysis of over 27,000 individual patients showed that pCR is associated with an event-free survival (EFS) of 90% vs. 57% in those with residual disease (HR 0.31, 95% CI 0.24–0.39) and overall survival (OS) of

94% vs. 75%, respectively (HR 0.22, 95% CI 0.15–0.30) [7]. This underscores the importance of pCR as the goal of NT.

Although a patient who achieves pCR is at low risk of relapse, it is important to note that pCR is not a surrogate marker for survival outcomes at a population level. A meta-analysis which specifically evaluated the relevant clinical outcomes of administering NT showed that pCR was not an accurate surrogate for EFS. Therefore, clinical trials evaluating NT still must include EFS and other relevant long-term survival outcomes as part of their follow up and statistical plans [8].

While there is prognostic value in administering NT and observing in vivo tumor response, one of the primary benefits of NT is to downstage a tumor. This approach can lead to better surgical outcomes and, in certain cases, make breast-conserving surgery (BCS) an option instead of requiring mastectomy. A recent observational study utilizing contemporary chemotherapy regimens found that NT prior to BCS was associated with lower re-excision rates, less margin positivity, and better patient satisfaction with cosmetic outcomes compared to women who underwent upfront surgery [9]. Another potential benefit of NT is de-escalation of axillary surgery in patients with clinically positive nodes at diagnosis. Contemporary studies and guidelines now support sentinel lymph node biopsy (SLNB) for most patients [10, 11]. In those with clinically positive lymph nodes who undergo NT and subsequently become clinically node negative, SLNB is considered a reasonable approach [12–16]. In the future, novel imaging techniques may be able to identify patients who have had a robust response to therapy, leading to additional de-escalation in surgical procedures and the ability to alter therapy quickly in those patients not having the expected imaging response [17].

Neoadjuvant Therapy in Triple-Negative Breast Cancer

TNBC is a heterogeneous group of breast cancers that do not express hormone receptors (ER or PR) and lack HER2 amplification. While these tumors are often grouped together in research studies and in clinical practice, individual tumors have unique characteristics that may determine prognosis and guide treatment choices. Typically, TNBC tumors are aggressive, with high proliferation rates, higher rates of recurrence, and poorer overall survival compared with hormone-receptor (HR) positive tumors. Cytotoxic chemotherapy remains the mainstay of curative-intent systemic therapy in early stage TNBC. For tumors > 1 cm, NT is strongly considered, for reasons described in the previous section. Contemporary regimens utilize a dose-dense polychemotherapy approach with granulocyte-colony stimulating factor support [18]. For patients who are less fit or have a history of cardiac disease, a non-anthracycline regimen such as docetaxel and cyclophosphamide (TC) or carboplatin and paclitaxel can be considered [19], especially for T1 tumors (≤ 2 cm) that are clinically node negative, where the benefit of anthracyclines appears to be small [20•]. Options for standard of care neoadjuvant therapy and risk-adapted adjuvant therapy are detailed in Fig. 1.

Platinum Chemotherapy

Several trials have investigated the addition of carboplatin to the standard anthracycline–taxane regimen, with most trials conducted in the neoadjuvant setting [21–30]. These trials are summarized in Table 1. The CALGB 40,603 trial investigated the impact of utilizing carboplatin and/or bevacizumab [24]. Using a 2 × 2 factorial design, patients were randomly

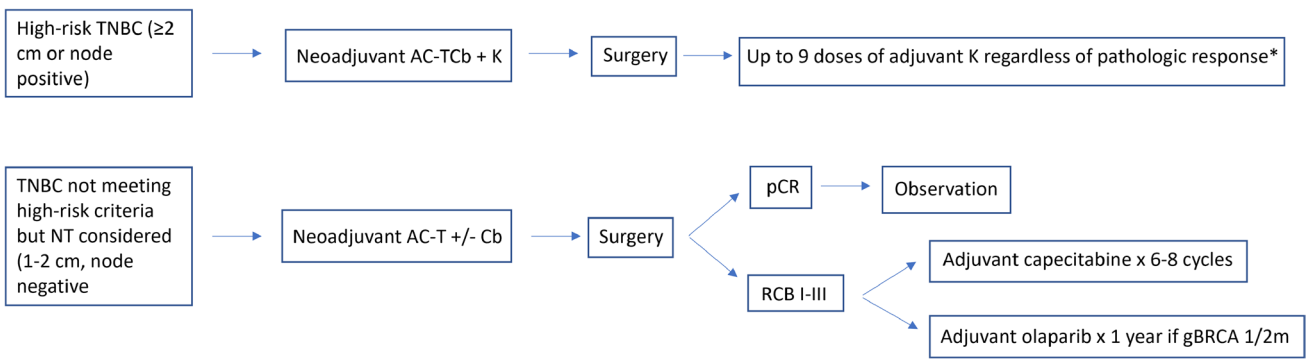

Fig. 1 Flow diagram of standard of care neoadjuvant therapy and risk-adapted adjuvant in TNBC. TNBC, triple negative breast cancer: A, doxorubicin; C, cyclophosphamide; T, paclitaxel; Cb, carboplatin; K, pembrolizumab; NT, neoadjuvant therapy; pCR, pathological complete response; RCB, residual cancer burden; gBRCA 1/2 m, germline BRCA 1 or 2 mutation. *Not known whether addition of adjuvant capecitabine in those with RCB I-III or adjuvant olaparib in gBRCA 1/2 m improves survival as KEYNOTE-522 did not include either

Table 1 Pathological complete response rates for randomized neoadjuvant trials investigating carboplatin in early-stage TNBC

Trial	Treatment	pCR	*p* value
GEICAM/2006–03	EC → T + / − Cb	30% in both arms	NA
Gepar-Sixto	LD + Pac + Bev + / − Cb	53.2% vs. 36.9%	0.005
Gepar-Octo	Pac + LD + Cb vs. E → Pac → C	51.7% vs. 48.5%	0.518
CALGB 40,603	Pac + / − Cb → ddAC + / − Bev	54% vs. 41%	0.0029
Ando et al	Pac + / − Cb → EC/5-FU	61.2% vs. 26.3%	0.003
Zhang et al	Pac + Cb vs. P + E	38.6% vs. 14%	0.014
WSG-ADAPT-TN	Nab-Pac + Cb vs. Nab-Pac + G	45.9% vs. 28.7%	0.002
BrighTNess	Cb + V + Pac → AC vs. Cb + Pac → AC vs. Pac → AC	53% vs. 58% vs. 31%	0.0001 (Cb + V + Pac vs. Pac)
NeoSTOP	Pac + Cb → AC vs. Cb + T	54% in both arms	NA
NeoCART	T + Cb vs. E + C → T	61.4% vs. 38.6%	0.004

E epirubicin, *C* cyclophosphamide, *T* docetaxel, *Cb* carboplatin, *LD* liposomal doxorubicin, *Pac* paclitaxel, *Bev* bevacizumab, *A* doxorubicin, *dd* dose dense, *G* gemcitabine, *V* veliparib

assigned to receive carboplatin + / − bevacizumab in addition to a standard dose-dense anthracycline–taxane backbone. Adding either agent increased the pCR rate, with 54% of those who received carboplatin achieving pCR compared to 41% in those who did not receive carboplatin (OR, 1.71; $p = 0.0029$). While the addition of bevacizumab numerically increased the pCR rate (52% vs. 44%), it was not statistically significant. There were more adverse effects (AEs) in those assigned to one or both investigational agents.

The GeparSixto trial investigated the addition of neoadjuvant carboplatin to anthracycline and paclitaxel chemotherapy in patients with TNBC or HER2 + subtypes. Patients in the TNBC group were also given bevacizumab and the HER2 + group was given trastuzumab and lapatinib. Of note, this is a non-standard backbone chemotherapy regimen, lacking use of cyclophosphamide. The investigators found that the addition of carboplatin significantly increased pCR in the TNBC group (53.2% vs. 36.9%, $p = 0.005$) but not in the HER2 + cohort [31]. After approximately 4-year follow-up, investigators found that in the TNBC cohort, the addition of carboplatin was associated with an improvement in disease-free survival (DFS) (HR = 0.56 [95% CI 0.34–0.93]) and distant disease-free survival (DDFS) (HR = 0.50 [95% CI 0.29–0.86]) while there was a trend toward better OS (HR = 0.60 [95% CI 0.32–1.12]). However, the carboplatin arm caused more toxicities and, consequently, a higher rate of treatment discontinuation. There were no survival differences in the HER2 + cohort [28].

In the BrighTNess trial, investigators evaluated differences in pCR and secondarily, survival outcomes, with the addition of both carboplatin and the poly(ADP-ribose) polymerase inhibitor (PARPi) veliparib. Patients with clinical stage II–III TNBC were randomized in a 2:1:1 fashion to one of three arms: paclitaxel/carboplatin/veliparib, paclitaxel/carboplatin/placebo, or paclitaxel/placebo/placebo. This was followed by anthracycline and cyclophosphamide × 4 cycles. The pCR rates were highest in the two carboplatin-containing arms, at 53% and 58%, respectively, compared with 31% in those who did not receive carboplatin ($p < 0.0001$) [22]. Updated results at a median of 4.5 years showed that EFS was improved with the triple combination compared to paclitaxel alone (HR 0.63; $p = 0.016$) but not when compared with the carboplatin/paclitaxel arm (HR 1.12; $p = 0.620$), suggesting that it is the carboplatin that had the larger impact [32]. There were more toxicities, serious AEs, and treatment discontinuations in the carboplatin-containing arms compared to paclitaxel alone.

The role of carboplatin in the neoadjuvant setting continues to be a debated topic, but with two large studies showing a benefit in EFS, the treatment paradigm is moving toward the inclusion of carboplatin as standard of care for early-stage TNBC. With that said, this benefit will need to be balanced with the increase in gastrointestinal and hematological toxicities that are common with this regimen and will inevitably lead to dose reduction, delays, or discontinuation in some patients. In fact, in both CALGB 40,603 and GeparSixto, the addition of platinum chemotherapy resulted in more frequent early discontinuation of taxane, leading investigators on BrighTNess to require making up missed doses of taxane. Importantly, there is also evidence showing that anthracycline-sparing regimens, such as carboplatin–docetaxel, result in a rate of pCR comparable to anthracycline-containing regimens [29].

The Addition of Checkpoint Inhibitors

Over the past 1–2 years, the use of CPI has emerged, with data from KEYNOTE-522 supporting the use of neoadjuvant and adjuvant pembrolizumab in combination with chemotherapy [33]. This randomized phase III study evaluated the use of PD-1 inhibitor pembrolizumab or placebo in combination with neoadjuvant chemotherapy,

consisting of paclitaxel–carboplatin followed by doxorubicin–cyclophosphamide. Following surgery, patients received adjuvant pembrolizumab or placebo. Results showed that significantly more patients in the pembrolizumab group achieved pCR (64.8% vs. 51.2%, $p < 0.001$). The data were updated after 3 years of follow-up, demonstrating a significant improvement in EFS with pembrolizumab (84.5% vs. 76.8%, $p < 0.001$) [34••]. Notably, the benefits in pCR and in EFS were seen in patients with both PD-L1 + and PD-L1 − tumors, suggesting that PD-L1 may not be an adequate biomarker to determine which patients will benefit from the addition of pembrolizumab in the neoadjuvant setting. In fact, a higher proportion of those with PD-L1 + tumors achieved pCR compared to the PD-L1 − cohort, regardless of whether they received pembrolizumab or placebo. Also notable was that patients with residual disease who had been enrolled in the pembrolizumab arm had an improved EFS compared to those with residual disease who received placebo, indicating that there may be a survival benefit to pembrolizumab regardless of whether pCR is achieved. This regimen is now FDA approved and is considered standard of care for clinically node-positive TNBC or clinically node-negative TNBC that is ≥ 2 cm in size.

IMpassion031 was a randomized phase III trial that investigated the use of the PD-L1 inhibitor atezolizumab versus placebo combined with nab-paclitaxel followed by doxorubicin–cyclophosphamide chemotherapy [35]. Atezolizumab was not continued adjuvantly. In the atezolizumab group, 58% of patients achieved pCR compared to 41% in the placebo group (17% difference, $p = 0.0044$). More patients with a PD-L1 + tumor achieved pCR compared to those with PD-L1 − tumors (69% vs. 49%, $p = 0.021$). Secondary endpoints included survival outcomes, which have not yet been reported.

Notably, in IMpassion031, PD-L1 expression was defined as ≥ 1% expression in tumor-infiltrating lymphocytes (TILs) covering ≥ 1% of the tumor area using the VENTANA SP142 assay. In KEYNOTE-522, PD-L1 testing was with the 22C3 pharmDx assay, and positive expression was defined as the number of PD-L1 + cells (tumor cells, lymphocytes, and macrophages) divided by the total number of tumor cells multiplied by 100. Tumors with a combined positive score (CPS) of ≥ 1 were considered PD-L1 + . The different assays and criteria for positivity demonstrate that the PD-L1 biomarker is not without controversy in interpretation and use.

Durvalumab has also been studied in this population. The GeparNuevo trial randomized patients with early-stage TNBC to nab-paclitaxel + / − durvalumab, a PD-L1 inhibitor. All patients went on to receive epirubicin and cyclophosphamide. Among the 174 patients enrolled, there was a numeric improvement in achievement of pCR (53.4% durvalumab group and 44.2% placebo group, $p = 0.224$) which was not statistically significant. Importantly, there was a subset of patients who received one dose of durvalumab prior to starting chemotherapy (window cohort). In this window cohort, there was a much higher and significant improvement in pCR rate compared to the non-window cohort (61% vs. 41%, $p = 0.035$) [36]. The 3-year invasive disease-free survival (iDFS) was higher in those who achieved pCR versus not [(92.0% vs. 71.9% (log-rank $p = 0.002$)]. The 3-year iDFS, DDFS, and OS were all significantly improved in the durvalumab group versus placebo [37]. There was no difference in survival outcomes between the window and non-window cohorts. These results are quite curious, as there was no statistically significant difference in pCR between the groups but significant improvements in survival outcomes, highlighting that some mechanisms of action of CPI are still incompletely understood and that pCR may not have the same prognostic utility in patients treated with CPI.

The NeoTRIP study evaluated the use of chemotherapy (carboplatin and nab-paclitaxel on days 1 and 8) + / − atezolizumab in patients with early-stage TNBC [38]. The pCR rate was 43.5% with atezolizumab and 40.8% without (OR 1.11, 95% CI 00.69–1.279). This was not a significant difference; however, the chemotherapy backbone that was used differed from standard practice and from other similar trials. The role of atezolizumab is currently being investigated in the phase III GeparDouze/NSABP B-59 trial (NCT03281954). Similar to KEYNOTE-522, patients will receive neoadjuvant atezolizumab or placebo with chemotherapy (carboplatin–paclitaxel followed by anthracycline–cyclophosphamide), followed by adjuvant atezolizumab.

Escalation of Adjuvant Therapy

As discussed previously, response to NT is an important outcome for an individual patient. In early-stage TNBC, residual disease is associated with a worse prognosis. Accordingly, trials in the last several years have attempted to improve upon this poorer prognosis, escalating adjuvant therapy for those with residual disease. The CREATE-X study is a phase III trial that investigated the use of adjuvant capecitabine for those with residual disease after NT. There was no requirement for ER status, but the treatment arms were balance adjusted for several factors including ER status. In the overall population, there was an improvement in both DFS (HR 0.70; 95% CI 0.53–0.92) and OS (HR for death, 0.59; 95% CI 0.39–0.90). However, when outcomes were evaluated by ER status, there remained a statistically significantly benefit in recurrence risk and survival only in the TNBC group, not the ER + group. The use of adjuvant capecitabine for TNBC patients with residual disease was subsequently considered standard of care.

More recent studies have looked to improve upon the outcomes from the CREATE-X trial by evaluating other agents,

such as platinum chemotherapy in the ECOG EA1131 trial, the PARPi olaparib in the OlympiA trial, and pembrolizumab in the BR006/S1418 trial, which finished its accrual in 2021. The ECOG EA1131 trial results revealed that in patients with clinical stage II–III TNBC and ≥ 1 cm of residual disease, platinum chemotherapy did not improve outcomes over capecitabine [39]. In contrast, the OlympiA study evaluated a more specific cohort of patients with a *BRCA 1/2* mutation and high-risk disease, including those with residual disease after NT. One year of adjuvant olaparib improved OS with a 32% reduction in the risk of death compared with placebo (stratified HR, 0.68; 98.5% CI 0.47–0.97; $p = 0.0009$). Adjuvant olaparib is now considered standard of care for this population of patients [40••, 41].

To date, there are no studies comparing adjuvant capecitabine to adjuvant olaparib in patients with a *BRCA 1/2* mutation, leaving clinicians in a data-free zone. However, as olaparib is a targeted therapy with known effectiveness over chemotherapy in the metastatic setting, it is often chosen over capecitabine in this population. Similarly, adjuvant capecitabine was not allowed in the KEYNOTE-522 trial and the results of OlympiA were not available until after KEYNOTE-522 was complete. Therefore, in patients who received the KEYNOTE-522 regimen, it is unknown whether escalating adjuvant therapy in those with residual disease to include capecitabine or olaparib in addition to or instead of pembrolizumab would improve outcomes.

Biomarkers of Response

Potentially important biomarkers in early-stage disease are the presence of PD-L1 on tumor cells and the presence of TILs in the stroma. The presence of TILs predicts for a more robust response to chemotherapy, achievement of pCR, and a better prognosis [42, 43], but currently is not a standard component of most pathology reports. The presence of TILs is not an indication for use of CPI, although both TILs and PD-L1 expression can indicate if a tumor is more likely to respond to CPI. In the early-stage setting, response to PD-1 inhibitors does not seem to be dependent on PD-L1 expression. In the KEYNOTE-522 study, even those who were PD-L1 negative benefited from the addition of pembrolizumab and achieved higher rates of pCR than PD-L1-negative patients who received placebo. Measuring expression of PD-L1 remains controversial with regard to determination of a positive test, antibody test of choice, and its utility as a predictive biomarker. There is also a lack of a linear correlation between level of PD-L1 expression and predicted response [44].

Molecular subtyping has shown that while grouped together by lack of standard biomarker expression, TNBC is not a homogeneous disease. Several classification systems for molecular gene signatures have been proposed, based on genomic profiling, and in the future may lead to more refined choices for systemic therapy. For example, Lehmann and colleagues describe several molecular subtypes including a basal-like subtype which showed higher gene expression related to cell proliferation and DNA damage response and was associated with a more robust response to NT including cisplatin. Other molecular subtypes were relatively more chemo-resistant and may respond better to immunotherapy or targeted agents [45]. Assays evaluating homologous repair deficiency (HRD) may also prove to be useful in identifying TNBC tumors in patients without a germline *BRCA* mutation but with molecular features similar to *BRCA* alterations. These tumors may be more susceptible to PARPi or to platinum chemotherapy.

Across breast cancer subtypes, circulating tumor DNA (ctDNA) is being investigated as a potential biomarker of response to therapy, allowing for early changes in therapy in those patients not experiencing clearance of ctDNA or escalation of adjuvant therapy for those with ctDNA detected after NT (NCT03145961, NCT03145961, NCT05333874). It may also have a role in surveillance and early detection of recurrence, although it is unknown whether early detection results in an improvement in survival [46]. Several studies are underway to try and understand the role of ctDNA in breast cancer diagnosis, treatment, and surveillance. The clinical utility of monitoring ctDNA in patients with breast cancer has not been established, and this practice is not recommended outside of a clinical trial.

Future Directions

Sacituzumab govitecan is an antibody–drug conjugate (ADC) targeting Trop-2 and is currently approved for pretreated metastatic TNBC. Trials are underway investigating this agent and other Trop-2 ADCs in neoadjuvant and adjuvant settings (NCT04230109, NCT04595565, NCT04434040). Several trials have investigated the use of neoadjuvant PARPi; however, at this time, the role of PARPi for NT of TNBC remains investigational [22, 47, 48]. Combining PARPi with platinum agents may be difficult given that both are DNA-damaging agents and the combination could increase hematological toxicity. Given the known activity of carboplatin in TNBC, more randomized trials combining carboplatin–taxane regimens (anthracycline-sparing) with CPI are also of great interest.

In addition to novel targeted therapy, innovative trial designs have begun to change the way that new therapeutic agents are evaluated, so that only the most promising continue through the trial process. This increases efficiency, minimizes costs, and facilitates access to potentially effective agents more quickly. The I-SPY 2 trial was the first of these "adaptive platform" trials, running multiple studies concurrently with a master protocol [49]. By utilizing an

adaptive trial design, agents that are unlikely to be effective are removed from the protocol while new agents are brought in. Studying novel investigational agents in the neoadjuvant setting allows for the primary endpoint of pCR to be evaluated relatively quickly, so that the protocol may be adapted based on probability of a particular agent's success.

Neoadjuvant Therapy in HER2 + Disease

Pivotal studies completed around the turn of the twenty-first century have established the crucial role of trastuzumab (H) in the treatment of HER2 + breast cancer. While HER2 + breast cancers are typically aggressive, higher-grade tumors, using chemotherapy in combination with HER2-targeted therapy has dramatically improved the prognosis. Similar to TNBC, early-stage HER2 + disease is commonly treated neoadjuvantly, especially with tumors ≥ 2 cm and when axillary lymph nodes are involved. Historically, chemotherapy regimens consisted of an anthracycline–taxane combination along with H. The combination of anthracycline with H, however, resulted in higher rates of cardiomyopathy and congestive heart failure (CHF). Consequently, non-anthracycline regimens have become more common. In addition, risk-adapted adjuvant therapy is now considered standard, with data supporting escalation of therapy in higher-risk situations. Patients with lower-risk cancers and those with robust responses to NT may be able to safely de-escalate therapy without compromising their outcome.

While several trials compared pCR rates using the HER2-targeted tyrosine kinase inhibitor (TKI) lapatinib in combination with H and/or chemotherapy, the addition of lapatinib was not found to improve survival outcomes and did not significantly improve pCR rates [50–52]. Consequently, standard NT does not currently include a TKI. Similarly, the ADC ado-trastuzumab emtansine (T-DM1) has been compared with standard chemotherapy in the neoadjuvant setting and did not improve pCR rate, although it was associated with less toxicity [53–55]. Small studies have evaluated T-DM1 in combination with other agents and have shown promising results, but currently T-DM1 does not have a clear role in NT. A flow diagram of standard neoadjuvant therapy and risk-adapted adjuvant therapy for HER2 + disease is shown in Fig. 2.

The Fading Role of Anthracycline and the Addition of Pertuzumab

While anthracycline chemotherapy was considered standard for many years in HER2 + disease, more recent trials have challenged this standard and shown that non-anthracycline regimens are associated with high pCR rates and similar survival outcomes. The BCIRG-006 trial was a pivotal phase III study that confirmed that H in combination with adjuvant chemotherapy results in an improvement in DFS and OS over chemotherapy alone and that the use of anthracycline (AC-TH, doxorubucin + cyclophosphamide followed by docetaxel + H) did not improve survival outcomes over a non-anthracycline regimen (TCH, docetaxel + carboplatin + H) [56]. While the incidence of high-grade CHF events was low, it was significantly more common among patients who received doxorubicin versus those who did not (2% vs. 0.4%, $p = 0.0005$). In addition, there were seven treatment-related leukemias in patients treated with AC-TH versus none in those treated with TCH.

As NT became more common, studies evaluating non-anthracycline regimens in this setting were done to evaluate pCR rates as well as survival outcomes and cardiomyopathy events. Pertuzumab (P), a novel HER2-targeted monoclonal antibody that inhibits dimerization of HER2 with other receptors, was also evaluated as an addition to standard curative-intent regimens after showing promising efficacy and negligible impact on cardiac outcomes in pre-clinical and early clinical studies. One of the first studies to evaluate P was the NeoSphere study, which investigated the use of H or P, or both, with docetaxel (T) as well as H and P without chemotherapy in the neoadjuvant setting [57]. Patients then underwent surgery and received 3 cycles of adjuvant 5-fluorouracil, epirubicin, and cyclophosphamide (FEC) chemotherapy except for the antibody-only neoadjuvant group who got T × 4 cycles followed by FEC × 3 cycles. The highest rate of pCR (45.8%) was in the group that received T, H, and P. The combination of H and T resulted in a pCR rate

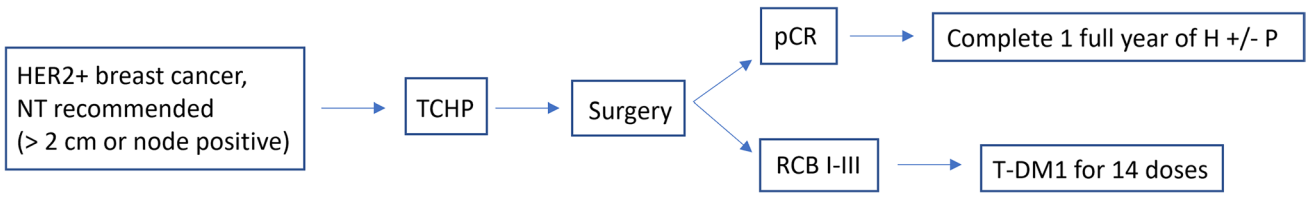

Fig. 2 Flow diagram of standard of care neoadjuvant therapy and risk-adapted adjuvant therapy in HER2 + disease. HER2 + : TCHP, docetaxel, carboplatin, trastuzumab, pertuzumab; NT, neoadjuvant therapy; pCR, pathologic complete response; RCB, residual cancer burden; T-DM1, ado-trastuzumab emtansine

of 29% and P and T of 24%. Interestingly, 17% of those who received antibody-only therapy achieved pCR. For some older or more frail patients, this non-chemotherapy regimen may be a reasonable approach.

The TRYPHAENA trial studied a similar regimen to BCIRG-006 (TCH) but added P to the regimen × 6 cycles (Arm C) compared with FEC + H + P × 3 cycles followed by T + H + P (arm A) or FEC × 3 cycles followed by T + H + P × 3 cycles (arm B) [58]. The primary outcome of this study was incidence of cardiomyopathy and systolic dysfunction while pCR was a secondary outcome. TCHP resulted in the highest rate of pCR (66.2%) compared to arm A (61.6%) and arm B (57.3%) and had the lowest incidence of a decline in left ventricular function at 3.9%, versus 5.6% (arm A) and 5.3% (arm B).

Most recently, the TRAIN-2 trial compared a regimen of FEC × 3 cycles followed by paclitaxel and carboplatin × 6 cycles to paclitaxel and carboplatin × 9 cycles, with all patients receiving H and P every 3 weeks [59••]. The primary endpoint was pCR. In the FEC group, 67% of patients achieved a pCR and in the paclitaxel/carboplatin group, 68% achieved a pCR. AEs were similar between the two groups, with the exceptions of a higher incidence of febrile neutropenia and a decline in LVEF in the FEC group. Survival outcomes were reported at 3 years and demonstrated no different in EFS or OS between the groups. Given these results, omission of anthracycline in the treatment of early-stage HER2 + breast cancer appears to be a safe and effective approach.

Escalation of Adjuvant Therapy

Adjuvant therapy in HER2 + disease can be escalated based on presence of residual disease after NT. The NSABP B-50 trial showed T-DM1 resulted in improved iDFS (HR 0.5, 95% CI 0.39–0.64, $p < 0.001$) and lower risk of distant recurrence (HR 0.60; 95% CI 0.45–0.79) compared to adjuvant trastuzumab [60•]. Use of adjuvant T-DM1 is now standard in this cohort of patients. Neratinib, an irreversible pan-HER TKI, is currently approved in the adjuvant setting for patients who have completed adjuvant H and has shown improvement in iDFS, particularly in those with HR + /HER2 + disease. There is also a suggestion of improvement in OS in patients with residual disease and a possible reduction in CNS events [61]. Neratinib has not been studied in patients who received adjuvant T-DM1 for residual disease nor has it been studied in those who received dual-targeted therapy with H and P. While its role in the context of current practice is thus unclear, it should still be a consideration in patients with HR + /HER2 co-expression and a high risk of relapse.

Biomarkers of Response

While several predictive biomarkers have been investigated in HER2 + disease, none have yet been confirmed to have utility in clinical decision-making or treatment choice. Nevertheless, certain biomarkers are associated with likelihood of pCR. For example, co-expression of HR with HER2 is associated with a lower chance of pCR. Combining HER2 and HR-targeted therapy has not yet proven to increase pCR rates, although there is some evidence that suggests that a longer duration of dual-targeted therapy may be more effective in this subset [55, 62, 63]. Another potential predictive biomarker is activation of the PIK3CA pathway, which is associated with resistance to HER2-targeted therapy and lower rate of pCR [64, 65]. Whether adding a PI3K inhibitor would overcome this resistance remains an open question, and the likely increase in toxicity would need to be considered [66]. Ki67 has also shown promise as a potential biomarker, with evidence showing that a robust drop in Ki67 (≥ 30%) during NT is predictive of achieving pCR [55]. Perhaps those who do not achieve this degree of Ki67 suppression are candidates for escalation of therapy. This approach is yet to be studied in the HER2 + population, although it has been evaluated in HR + neoadjuvant endocrine therapy trials. Molecular assays such as PAM50 intrinsic subtyping may prove to be useful in identifying tumors that are HER2 enriched, which is predictive of higher pCR rate [67]. A small phase II study, PAMELA, showed that patients with HER2-enriched tumors had a higher pCR rate than other intrinsic subtypes with a combination of lapatinib and H + / − endocrine therapy (non-chemotherapy regimen). Investigators also showed that presence of on-treatment TILs (assessed at baseline and at day 14 biopsy) were associated with a higher response rate [68, 69].

Future Directions

While achieving optimal outcomes for every patient with HER2 + disease is the goal, this should be balanced with the risk of long- and short-term treatment-related AEs, such as neuropathy, CHF, severe hematological toxicity, and gastrointestinal toxicity. With this in mind, many trials in the HER2 + space are now evaluating escalation/de-escalation type designs, attempting to limit AEs while maximizing response and efficacy. The CompassHER2-pCR trial (NCT04266249) is investigating the combination of taxane chemotherapy + HP, de-escalating by omitting standard carboplatin. If patients achieve pCR, they go on to complete adjuvant HP; if not, they receive T-DM1 and/or additional chemotherapy. The DESCRESCENDO trial (NCT04675827) is a de-escalation/escalation trial similar to CompassHER2-pCR. The escalation trial CompassHER2-RD (NCT04457596) is designed to evaluate adjuvant

Table 2 Ongoing trials in early-stage HER2 + breast cancer

Trial	Trial setting	Trial arms
CompassHER2-pCR trial	Neoadjuvant/adjuvant	THP → HP (pCR) vs. THP → TDM1 + / − more chemotherapy (no pCR)
DECRESCENDO	Neoadjuvant/adjuvant	THP → HP (pCR) vs. THP → TDM1 + / − more chemotherapy (no pCR)
APTNeo	Neoadjuvant	Atezo + Pac + Cb + HP
neoHIP	Neoadjuvant	Pembro + Pac + HP
Destiny-Breast11	Neoadjuvant	T-Dxd alone or followed by chemotherapy

T taxane, *H* trastuzumab, *P* pertuzumab, *TDM1* ado-trastuzumab emtansine, *Atezo* atezolizumab, *Pac* paclitaxel, *Cb* carboplatin, *Pembro* pembrolizumab, *T-Dxd* trastuzumab deruxtecan

T-DM1 in combination with tucatinib compared with T-DM1 and placebo (standard comparator arm). Destiny-Breast05 (NCT04622319) is investigating the ADC trastuzumab deruxtecan (T-Dxd) as adjuvant therapy for patients with residual disease compared to standard T-DM1. T-Dxd is also under investigation as NT, either alone or in sequence with standard therapy (NCT05113251).

Several trials are evaluating the addition of CPI therapy, although its role in HER2 + disease is not established, in contrast to TNBC. Notably, the Impassion050 trial investigated atezolizumab versus placebo in patients receiving standard dose-dense anthracycline and taxane-based chemotherapy with H and P. Patients then continued atezolizumab with standard adjuvant therapy. The trial was stopped early due to safety concerns, with four deaths on the investigational arm, two attributed to study treatment. In addition, the pCR rates between the groups were found to be no different (62.4% with atezolizumab, 62.7% with placebo) [70]. Other neoadjuvant trials evaluating atezolizumab are ongoing. The APTneo trial (NCT03595592) is evaluating atezolizumab, H, and P with paclitaxel and carboplatin as NT while the Astefania trial (NCT04873362) combines atezolizumab with adjuvant T-DM1 compared with T-DM1 and placebo in high-risk patients. Pembrolizumab is also being evaluated in the neoadjuvant space, with the neoHIP trial (NCT03747120) investigating the addition of pembrolizumab to paclitaxel + HP. Neoadjuvant trials are summarized in Table 2. While PD-L1 and other biomarkers are being evaluated as part of these studies, biomarkers of response to CPI in HER2 + disease are even less clear than in TNBC.

Conclusion

NT has proven an effective way to provide important prognostic information using the RCB and has allowed clinicians to provide a refined, risk-adapted approach to adjuvant therapy. As new agents and combinations continue to improve response rates and survival outcomes, it is critical to concurrently evaluate predictive biomarkers to identify patients most likely to respond. In addition, studies investigating novel imaging techniques should be a priority, to provide opportunity for early modifications in patients not adequately responding. These, and other advancements, will continue to lead us from the early phases of precision medicine to increasingly individualized care.

Declarations

Conflict of Interest The author has research support from Laekna, Pfizer, AstraZeneca, and Hoffman-La Roche. There are no competing interests with regard to this manuscript.

References

Papers of particular interest, published recently, have been highlighted as:
- • Of importance
- •• Of major importance

1. G Early Breast Cancer Trialists' Collaborative. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. Lancet Oncol. 2018;19(1):27–39.
2. Xia L-Y, Hu Q-L, Zhang J, Xu W-Y, Li X-S. Survival outcomes of neoadjuvant versus adjuvant chemotherapy in triple-negative breast cancer: a meta-analysis of 36,480 cases. World J Surgical Oncol. 2020;18(1):129.
3. Symmans WF, Wei C, Gould R, et al. Long-term prognostic risk after neoadjuvant chemotherapy associated with residual cancer burden and breast cancer subtype. J Clin Oncol: Off J Am Soc Clin Oncol. 2017;35(10):1049–60.
4. Yau C, Osdoit M, van der Noordaa M, et al. Residual cancer burden after neoadjuvant chemotherapy and long-term survival outcomes in breast cancer: a multicentre pooled analysis of 5161 patients. Lancet Oncol. 2022;23(1):149–60.
5. Symmans WF, Yau C, Chen Y-Y, et al. Assessment of residual cancer burden and event-free survival in neoadjuvant treatment

for high-risk breast cancer: an analysis of data from the I-SPY2 randomized clinical trial. JAMA Oncol. 2021;7(11):1654–63.
6. Hamy AS, Darrigues L, Laas E, et al. Prognostic value of the Residual Cancer Burden index according to breast cancer subtype: validation on a cohort of BC patients treated by neoadjuvant chemotherapy. PLoS One. 2020;15(6):e0234191.
7. Spring LM, Fell G, Arfe A, et al. Pathologic complete response after neoadjuvant chemotherapy and impact on breast cancer recurrence and survival: a comprehensive meta-analysis. Clin Cancer Res: Off J Am Assoc Cancer Res. 2020;26(12):2838–48.
8. 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):164–72.
9. Woeste MR, Bhutiani N, Donaldson M, McMasters KM, Ajkay N. Evaluating the effect of neoadjuvant chemotherapy on surgical outcomes after breast conserving surgery. J Surg Oncol. 2021;123(2):439–45.
10. Krag DN, Anderson SJ, Julian TB, et al. Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: overall survival findings from the NSABP B-32 randomised phase 3 trial. Lancet Oncol. 2010;11(10):927–33.
11. Giuliano AE, Ballman KV, McCall L, et al. Effect of axillary dissection vs no axillary dissection on 10-year overall survival among women with invasive breast cancer and sentinel node metastasis: the ACOSOG Z0011 (Alliance) Randomized Clinical Trial. JAMA. 2017;318(10):918–26.
12. 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.
13. Classe JM, Loaec C, Gimbergues P, et al. Sentinel lymph node biopsy without axillary lymphadenectomy after neoadjuvant chemotherapy is accurate and safe for selected patients: the GANEA 2 study. Breast Cancer Res Treat. 2019;173(2):343–52.
14. 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: Off J Am Soc Clin Oncol. 2015;33(3):258–64.
15. 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.
16. Brackstone M, Baldassarre FG, Perera FE, et al. Management of the axilla in early-stage breast cancer: Ontario Health (Cancer Care Ontario) and ASCO Guideline. J Clin Oncol. 2021;39(27):3056–82.
17. Rauch GM, Adrada BE, Kuerer HM, van la Parra RFD, Leung JWT, Yang WT. Multimodality imaging for evaluating response to neoadjuvant chemotherapy in breast cancer. Am J Roentgenol. 2016;208(2):290–9.
18. Citron ML, Berry DA, Cirrincione C, et al. Randomized trial of dose-dense versus conventionally scheduled and sequential versus concurrent combination chemotherapy as postoperative adjuvant treatment of node-positive primary breast cancer: first report of Intergroup Trial C9741/Cancer and Leukemia Group B Trial 9741. J Clin Oncol: Off J Am Soc Clin Oncol. 2003;21(8):1431–9.
19. Yu K-D, Ye F-G, He M, et al. Effect of adjuvant paclitaxel and carboplatin on survival in women with triple-negative breast cancer: a phase 3 randomized clinical trial. JAMA Oncol. 2020;6(9):1390–6.
20.• Blum JL, Flynn PJ, Yothers G, et al. Anthracyclines in early breast cancer: The ABC Trials—USOR 06–090, NSABP B-46-I/USOR 07132, and NSABP B-49 (NRG Oncology). J ClinOncol. 2017;35(23):2647–2655. **This clinical trial examined an anthracycline-containing adjuvant chemotherapy regimen compared with a non-anthracycline regimen. Exploratory analyses suggested a small benefit of anthracyclines in patients with node-negative early-stage TNBC and a larger benefit in those with node-positive TNBC.**
21 Alba E, Chacon JI, Lluch A, et al. A randomized phase II trial of platinum salts in basal-like breast cancer patients in the neoadjuvant setting. Results from the GEICAM/2006–03, multicenter study. Breast Cancer Res Treat. 2012;136(2):487–93.
22. Loibl S, O'Shaughnessy J, Untch M, et al. Addition of the PARP inhibitor veliparib plus carboplatin or carboplatin alone to standard neoadjuvant chemotherapy in triple-negative breast cancer (BrighTNess): a randomised, phase 3 trial. Lancet Oncol. 2018;19(4):497–509.
23. Schneeweiss A, Möbus V, Tesch H, et al. Intense dose-dense epirubicin, paclitaxel, cyclophosphamide versus weekly paclitaxel, liposomal doxorubicin (plus carboplatin in triple-negative breast cancer) for neoadjuvant treatment of high-risk early breast cancer (GeparOcto-GBG 84): a randomised phase III trial. Eur J Cancer (Oxford, England : 1990). 2019;106:181–92.
24. Shepherd JH, Ballman K, Polley MC, et al. CALGB 40603 (Alliance): long-term outcomes and genomic correlates of response and survival after neoadjuvant chemotherapy with or without carboplatin and bevacizumab in triple-negative breast cancer. J Clin Oncol: Off J Am Soc Clin Oncol. 2022;Jco2101506.
25. Ando M, Yamauchi H, Aogi K, et al. Randomized phase II study of weekly paclitaxel with and without carboplatin followed by cyclophosphamide/epirubicin/5-fluorouracil as neoadjuvant chemotherapy for stage II/IIIA breast cancer without HER2 overexpression. Breast Cancer Res Treat. 2014;145(2):401–9.
26. Zhang P, Yin Y, Mo H, et al. Better pathologic complete response and relapse-free survival after carboplatin plus paclitaxel compared with epirubicin plus paclitaxel as neoadjuvant chemotherapy for locally advanced triple-negative breast cancer: a randomized phase 2 trial. Oncotarget. 2016;7(37):60647–56.
27. Gluz O, Nitz U, Liedtke C, et al. Comparison of neoadjuvant nab-paclitaxel+carboplatin vs nab-paclitaxel+gemcitabine in triple-negative breast cancer: randomized WSG-ADAPT-TN Trial results. J Natl Cancer Inst. 2018;110(6):628–37.
28. Untch M, Schneeweiss A, Salat C, et al. Long-term survival analysis of the randomized phase II trial investigating the addition of carboplatin to neoadjuvant therapy for triple-negative (TNBC) and HER2-positive early breast cancer (GeparSixto). Ann Oncol. 2017;28:v49.
29. Sharma P, Kimler BF, O'Dea A, et al. Randomized phase II trial of anthracycline-free and anthracycline-containing neoadjuvant carboplatin chemotherapy regimens in stage I-III triple-negative breast cancer (NeoSTOP). Clin Cancer Res: Off J Am Assoc Cancer Res. 2021;27(4):975–82.
30. Zhang L, Wu ZY, Li J, et al. Neoadjuvant docetaxel plus carboplatin vs epirubicin plus cyclophosphamide followed by docetaxel in triple-negative, early-stage breast cancer (NeoCART): results from a multicenter, randomized controlled, open-label phase II trial. Int J Cancer. 2022;150(4):654–62.
31. 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.
32. Geyer CE, Sikov WM, Huober J, et al. Long-term efficacy and safety of addition of carboplatin with or without veliparib to standard neoadjuvant chemotherapy in triple-negative breast cancer: 4-year follow-up data from BrighTNess, a randomized phase III trial. Ann Oncol. 2022;33(4):384–94.
33. Schmid P, Cortes J, Pusztai L, et al. Pembrolizumab for early triple-negative breast cancer. N Engl J Med. 2020;382(9):810–21.

34.•• Schmid P CJ, Dent R, et al. KEYNOTE-522: Phase 3 study of neoadjuvant pembrolizumab plus chemotherapy versus placebo plus chemotherapy, followed by adjuvant pembrolizumab versus placebo for early-stage triple-negative breast cancer. ESMO Virtual Plenary Abstract VP7–2021. Presented July 15, 2021.**This clinical trial established a new standard of care for high-risk TNBC, confirming that pembrolizumab increased the chance of pCR in combination with chemotherapy and resulted in improvement in EFS. This regimen is now standard of care in this population.**

35. Mittendorf EA, Zhang H, Barrios CH, et al. Neoadjuvant atezolizumab in combination with sequential nab-paclitaxel and anthracycline-based chemotherapy versus placebo and chemotherapy in patients with early-stage triple-negative breast cancer (IMpassion031): a randomised, double-blind, phase 3 trial. Lancet. 2020;396(10257):1090–100.

36. Loibl S, Untch M, Burchardi N, et al. A randomised phase II study investigating durvalumab in addition to an anthracycline taxane-based neoadjuvant therapy in early triple-negative breast cancer: clinical results and biomarker analysis of GeparNuevo study. Ann Oncol: Off J Eur Soc Med Oncol. 2019;30(8):1279–88.

37. Loibl S, Schneeweiss A, Huober JB, et al. Durvalumab improves long-term outcome in TNBC: results from the phase II randomized GeparNUEVO study investigating neodjuvant durvalumab in addition to an anthracycline/taxane based neoadjuvant chemotherapy in early triple-negative breast cancer (TNBC). J Clin Oncol. 2021;39(15_suppl):506.

38. Gianni L, Huang CS, Egle D, et al. Pathologic complete response (pCR) to neoadjuvant treatment with or without atezolizumab in triple-negative, early high-risk and locally advanced breast cancer: NeoTRIP Michelangelo randomized study. Annals Oncol: Off J Eur Soc Med Oncol. 2022.

39. Mayer IA, Zhao F, Arteaga CL, et al. Randomized phase III postoperative trial of platinum-based chemotherapy versus capecitabine in patients with residual triple-negative breast cancer following neoadjuvant chemotherapy: ECOG-ACRIN EA1131. J Clin Oncol. 2021;39(23):2539–51.

40.•• Tutt ANJ, Garber JE, Kaufman B, et al. Adjuvant olaparib for patients with BRCA1- or BRCA2-mutated breast cancer. New England J Med. 2021;384(25):2394–2405. **This clinical trial showed that in patients with a BRCA 1 or 2 mutation and HER2-negative, high-risk early-stage breast cancer, olaparib improves OS compared to placebo and is now standard of care for these patients.**

41. Abstract VP1-2022: Pre-specified event driven analysis of Overall Survival (OS) in the OlympiA phase III trial of adjuvant olaparib (OL) in germline BRCA1/2 mutation (gBRCAm) associated breast cancer. March 16, 2022.ESMO Virtual Plenary.

42. Demaria S, Volm MD, Shapiro RL, et al. Development of tumor-infiltrating lymphocytes in breast cancer after neoadjuvant paclitaxel chemotherapy. Clin Cancer Res: Off J Am Assoc Cancer Res. 2001;7(10):3025–30.

43. Loi S, Sirtaine N, Piette F, et al. Prognostic and predictive value of tumor-infiltrating lymphocytes in a phase III randomized adjuvant breast cancer trial in node-positive breast cancer comparing the addition of docetaxel to doxorubicin with doxorubicin-based chemotherapy: BIG 02–98. J Clin Oncol: Off J Am Soc Clin Oncol. 2013;31(7):860–7.

44. Sun WY, Lee YK, Koo JS. Expression of PD-L1 in triple-negative breast cancer based on different immunohistochemical antibodies. J Transl Med. 2016;14(1):173.

45. Lehmann BD, Jovanović B, Chen X, et al. Refinement of triple-negative breast cancer molecular subtypes: implications for neoadjuvant chemotherapy selection. PLoS One. 2016;11(6):e0157368.

46. Cullinane C, Fleming C, O'Leary DP, et al. Association of circulating tumor DNA with disease-free survival in breast cancer: a systematic review and meta-analysis. JAMA Netw Open. 2020;3(11):e2026921–e2026921.

47. Fasching PA, Link T, Hauke J, et al. Neoadjuvant paclitaxel/olaparib in comparison to paclitaxel/carboplatinum in patients with HER2-negative breast cancer and homologous recombination deficiency (GeparOLA study). Ann Oncol: Off J Eur Soc Med Oncol. 2021;32(1):49–57.

48. Rugo HS, Olopade OI, DeMichele A, et al. Adaptive randomization of veliparib-carboplatin treatment in breast cancer. N Engl J Med. 2016;375(1):23–34.

49. Wang H, Yee D. I-SPY 2: a neoadjuvant adaptive clinical trial designed to improve outcomes in high-risk breast cancer. Curr Breast Cancer Rep. 2019;11(4):303–10.

50. Robidoux A, Tang G, Rastogi P, et al. Lapatinib as a component of neoadjuvant therapy for HER2-positive operable breast cancer (NSABP protocol B-41): an open-label, randomised phase 3 trial. Lancet Oncol. 2013;14(12):1183–92.

51. 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.

52. Carey LA, Berry DA, Cirrincione CT, et al. Molecular heterogeneity and response to neoadjuvant human epidermal growth factor receptor 2 targeting in CALGB 40601, a randomized phase III trial of paclitaxel plus trastuzumab with or without lapatinib. J Clin Oncol: Off J Am Soc Clin Oncol. 2016;34(6):542–9.

53. 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.

54. Hatschek T, Foukakis T, Bjöhle J, et al. Neoadjuvant trastuzumab, pertuzumab, and docetaxel vs trastuzumab emtansine in patients with ERBB2-positive breast cancer: a phase 2 randomized clinical trial. JAMA Oncol. 2021;7(9):1360–7.

55. Harbeck N, Gluz O, Christgen M, et al. De-Escalation strategies in human epidermal growth factor receptor 2 (HER2)-positive early breast cancer (BC): final analysis of the West German Study Group Adjuvant Dynamic Marker-Adjusted Personalized Therapy Trial Optimizing Risk Assessment and Therapy Response Prediction in Early BC HER2- and Hormone Receptor-Positive Phase II Randomized Trial-Efficacy, Safety, and Predictive Markers for 12 Weeks of Neoadjuvant Trastuzumab Emtansine With or Without Endocrine Therapy (ET) Versus Trastuzumab Plus ET. J Clin Oncol: Off J Am Soc Clin Oncol. 2017;35(26):3046–54.

56. Slamon D, Eiermann W, Robert N, et al. Adjuvant trastuzumab in HER2-positive breast cancer. N Engl J Med. 2011;365(14):1273–83.

57. 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.

58. Schneeweiss A, Chia S, Hickish T, et al. Pertuzumab plus trastuzumab in combination with standard neoadjuvant anthracycline-containing and anthracycline-free chemotherapy regimens in patients with HER2-positive early breast cancer: a randomized phase II cardiac safety study (TRYPHAENA). Ann Oncol. 2013;24(9):2278–84.

59.•• van der Voort A, van Ramshorst MS, van Werkhoven ED, et al. Three-year follow-up of neoadjuvant chemotherapy with or without anthracyclines in the presence of dual ERBB2 blockade in patients with ERBB2-positive breast cancer: a secondary analysis of the TRAIN-2 randomized, phase 3 trial. JAMA Oncol. 2021;7(7):978–984. **This clinical trial compared an anthracycline-containing regimen vs a non-anthracycline regimen in combination with HER2-directed therapy in HER2+ early-stage breast cancer patients. Investigators found that 3-year EFS was no different between the study arms and that a decline in LVEF was more common in those who received anthracyclines.**

60.• von Minckwitz G, Huang C-S, Mano MS, et al. Trastuzumab emtansine for residual invasive HER2-positive breast cancer. New England J Med. 2018;380(7):617–628. **This clinical trial confirmed that adjuvant T-DM1 results in superior iDFS compared with adjuvant trastuzumab in patients with HER2+ breast cancer and residual disease after NT. T-DM1 is now standard adjuvant therapy for these patients.**

61. Chan A, Moy B, Mansi J, et al. Final efficacy results of neratinib in HER2-positive hormone receptor-positive early-stage breast cancer from the phase III ExteNET trial. Clin Breast Cancer. 2021;21(1):80-91.e87.

62. Rimawi MF CR, Rastogi P, Geyer, Jr CE, Fehrenbacher L, Stella PJ, Dayao Z, Rabinovitch R, Dyar SH, Flynn PJ, Baez-Diaz L, Paik S, Swain SM, Mamounas EP, Osborne CK, Wolmark N. A phase III trial evaluating pCR in patients with HR+, HER2-positive breast cancer treated with neoadjuvant docetaxel, carboplatin, trastuzumab, and pertuzumab (TCHP) +/− estrogen deprivation: NRG Oncology/NSABP B-52 [abstract]. In: Proceedings of the 2016 San Antonio Breast Cancer Symposium. 2016;Dec 6–10; San Antonio, TX. Philadelphia (PA): AACR; Cancer Res 2017;77(4 Suppl):Abstract nr S3–06.

63. Rimawi MF, Niravath P, Wang T, et al. TBCRC023: a randomized phase II neoadjuvant trial of lapatinib plus trastuzumab without chemotherapy for 12 versus 24 weeks in patients with HER2-positive breast cancer. Clin Cancer Res: Off J Am Assoc Cancer Res. 2020;26(4):821–7.

64. Fan H, Li C, Xiang Q, et al. PIK3CA mutations and their response to neoadjuvant treatment in early breast cancer: a systematic review and meta-analysis. Thoracic cancer. 2018;9(5):571–9.

65. Loibl S, Majewski I, Guarneri V, et al. PIK3CA mutations are associated with reduced pathological complete response rates in primary HER2-positive breast cancer: pooled analysis of 967 patients from five prospective trials investigating lapatinib and trastuzumab. Ann Oncol: Off J Eur Soc Med Oncol. 2016;27(8):1519–25.

66. André F, O'Regan R, Ozguroglu M, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2014;15(6):580–91.

67. Schettini F, Pascual T, Conte B, et al. HER2-enriched subtype and pathological complete response in HER2-positive breast cancer: a systematic review and meta-analysis. Cancer Treat Rev. 2020;84:101965.

68. Nuciforo P, Pascual T, Cortés J, et al. A predictive model of pathologic response based on tumor cellularity and tumor-infiltrating lymphocytes (CelTIL) in HER2-positive breast cancer treated with chemo-free dual HER2 blockade. Ann Oncol: Off J Eur Soc Med Oncol. 2018;29(1):170–7.

69. Llombart-Cussac A, Cortés J, Paré L, et al. HER2-enriched subtype as a predictor of pathological complete response following trastuzumab and lapatinib without chemotherapy in early-stage HER2-positive breast cancer (PAMELA): an open-label, single-group, multicentre, phase 2 trial. Lancet Oncol. 2017;18(4):545–54.

70. Huober J, Barrios CH, Niikura N, et al. VP6-2021: IMpassion050: a phase III study of neoadjuvant atezolizumab + pertuzumab + trastuzumab + chemotherapy (neoadj A + PH + CT) in high-risk, HER2-positive early breast cancer (EBC). Ann Oncol. 2021;32(8):1061–2.