Review Article

The neoadjuvant systemic treatment of early breast cancer: a narrative review

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Background and Objective: The use of neoadjuvant systemic therapy for breast cancer is on the rise. Neoadjuvant treatment is equally effective as adjuvant treatment in preventing disease recurrence and death. The role of neoadjuvant treatment is unique for each breast cancer subtype. Neoadjuvant systemic therapy can improve surgical outcomes, provide valuable prognostic information and the response can guide post operative systemic treatment decisions. There is a growing need for all disciplines involved in the treatment of early breast cancer to discuss with patients the potential role of neoadjuvant treatment for their tumor subtype. To better guide the use of neoadjuvant systemic treatment we aim to detail its unique role in the three breast cancer subtypes with a focus on patient selection, surgical and oncological benefits, and future directions.

Methods: We performed a search of the PubMed, Cochrane Review, and Clinical Trials.gov databases. We used the search terms "neoadjuvant chemotherapy" AND "breast cancer" and then conducted a thorough manual review of all bibliographies and relevant studies to identify additional potentially eligible studies.

Key Content and Findings: To improve surgical outcomes, neoadjuvant therapy can be considered in all patients with operable breast cancer deemed to require adjuvant systemic treatment. For patients with human epidermal growth factor receptor-2 (HER-2) positive and triple negative breast cancer (TNBC) the presence of residual tumor can prompt a postoperative treatment change. For postmenopausal women with hormone receptor (HR) positive HER-2 negative tumors neoadjuvant endocrine treatment should be considered to help facilitate breast conservation. The use of preoperative gene expression profiles can be considered to decide whether to administer neoadjuvant chemotherapy (NACT) to patients with HR positive HER-2 negative tumors who require mastectomy or axillary lymph node dissection (ALND) upfront, however the role of these tests in the neoadjuvant setting is still unclear. Neoadjuvant therapy offers a unique window of opportunity to research additional biomarkers and systemic treatments.

Conclusions: The role of neoadjuvant systemic therapy in early breast cancer is continuing to develop with the likelihood that its applications will continue to expand, further emphasizing the importance of multidisciplinary communication to provide the best outcomes for our patients.

Keywords: Neoadjuvant; pathological complete response (pCR); triple negative (TN); human epidermal growth factor receptor-2 positive (HER-2 positive); hormone receptor positive (HR positive)

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Introduction

Over the last decade, the use of neoadjuvant chemotherapy (NACT) for the treatment of early breast cancer, particularly locally advanced breast cancers, has significantly increased (1). There is a growing need for all disciplines involved in the treatment of early breast cancer to understand and discuss with patients the potential role of neoadjuvant treatment for their tumor subtype. Results of the NSABP-B18 trial demonstrated that NACT provides similar disease-free survival (DFS) and overall survival (OS) as adjuvant chemotherapy. Patients receiving NACT experienced an increased likelihood of breast conserving surgery (BCS) and of pathologically negative nodes (2). A 2018 meta-analysis by the early breast cancer trialists collaborative group (EBCTCG) showed that NACT increases BCS rates compared to adjuvant chemotherapy (3). NACT may also spare clinically node positive patients the long-term morbidity associated with an axillary lymph node dissection (ALND). The SENTINA (4) and ACOSOG Z1071 trial (5) showed that clinically node positive patients who respond to NACT can be accurately staged by sentinel lymph node biopsy (SLNB) alone and the use of dual tracers and removal of at least three sentinel nodes provides a clinically acceptable false negative rate (FNR) of <10%, while placing a clip in the biopsy proven node and removing it at surgery further reduces the FNR (6). Beyond surgical advantages, neoadjuvant systemic therapy provides important prognostic information. A pooled analysis of 12 neoadjuvant trials involving almost 12,000 patients showed that on an individual patient level a pathological complete response (pCR) defined as no residual invasive tumor in the breast or lymph nodes was significantly associated with event free survival (EFS) and OS (7). This association was strongest in patients with human epidermal growth factor receptor-2 (HER-2) positive and triple negative (TN) tumors compared to hormone receptor (HR) positive tumors. While pCR is dichotomous, a graded index known as the residual cancer burden (RCB) has also been shown to be prognostic of long term survival (8) with pCR classified as RCB-0, minimal residual disease as RCB-1, moderate residual disease as RCB-2 and extensive residual disease as RCB-3 (9). This index has also been shown to be continuously prognostic independent of other clinicopathological variables for 10-year relapse free survival in all 3 breast cancer subtypes, with a greater prognostic impact in the TN and HER-2 positive subtypes (8). The prognostic insight provided by pCR has been translated into positive postoperative treatment escalation studies using residual disease to predict which patients may benefit from additional postoperative systemic therapy (10,11). The primary surgical and oncological advantages of neoadjuvant systemic treatment are shown in *Table 1*. Ancillary advantages of neoadjuvant treatment include increased time for genetic testing and consideration of reconstructive or prophylactic surgical options prior to breast surgery. Despite the adoption of a multidisciplinary approach to the treatment of early breast cancer, for many patients it is still unclear who stands to benefit most from a neoadjuvant approach, limiting its clinical implementation. In this review we aim to provide all clinicians involved in the treatment of early breast cancer with a comprehensive assessment of the role of neoadjuvant systemic therapy in HR positive, HER-2 positive and TN breast cancer, focusing on patient selection, surgical and oncological benefits, and future directions. We present the following article in accordance with the Narrative Review reporting checklist (available at https://abs.amegroups.com/article/view/10.21037/abs-21-109/rc).

Methods

We performed a search of the PubMed, Cochrane Review, and Clinical Trials.gov databases. Only English language publications were included. The search terms were as follows: “neoadjuvant chemotherapy” AND “breast cancer”. We conducted a thorough manual review of all bibliographies and relevant studies to identify additional potentially eligible studies (*Table 2*).

HER-2 positive breast cancer

Anti-HER-2 therapy administered with chemotherapy in patients with HER-2 positive breast cancer has led to a significant reduction in tumor recurrence and death, and when given preoperatively, is associated with high rates of pCR (12,13). Nevertheless, not all patients require such intensive treatment and de-escalation of anti-HER-2 targeted therapies and chemotherapy in appropriately selected populations has been an area of increased research. Currently, patients with stage 1 HER-2 positive breast cancer have excellent outcomes with adjuvant single agent paclitaxel and trastuzumab (14) and unless breast tumor downstaging is required to optimize surgery these patients do not require neoadjuvant treatment. Neoadjuvant treatment can be considered in all medically fit patients with stage 2 or 3 HER-2 positive breast cancer regardless of their pretreatment eligibility for BCS as their response to

Table 1 Goals of neoadjuvant systemic treatment

1. Improve patient DFS and OS similarly to adjuvant therapy
2. Improve surgical outcomes (breast conservation rates, spare axillary dissection)
3. Provide prognostic information
4. Enable escalation or de-escalation of postoperative systemic treatment

DFS, disease-free survival; OS, overall survival.

neoadjuvant treatment may affect postoperative treatment decisions (15).

Pivotal trials

The adjuvant NSABP B-31/NCCTG-N9831 trials demonstrated that the addition of one year of trastuzumab to anthracycline/taxane based chemotherapy resulted in a 40% reduction in breast cancer recurrences and a 37% reduction in mortality (12). Following the success of trastuzumab in the adjuvant setting, phase 2 trials showed impressive pCR rates in the neoadjuvant setting in patients with stage 2 and 3 HER-2 positive breast cancer treated with trastuzumab and chemotherapy (15-17). In the phase 3 NOAH (Neoadjuvant Herceptin) trial the addition of trastuzumab to chemotherapy yielded a response rate of 81% and a significantly superior pCR rate compared to chemotherapy alone (13) translating into a 36% relative improvement in 5-year EFS (18). The HER-2 dimerization inhibitor pertuzumab further improved outcomes when incorporated into both neoadjuvant and adjuvant trastuzumab/chemotherapy regimens and received accelerated approval in the neoadjuvant setting based largely on data from the phase 2 NeoSphere trial (19,20). This trial compared pCR rates between docetaxel/trastuzumab/pertuzumab (THP), docetaxel/trastuzumab (TH), docetaxel/pertuzumab (TP) and trastuzumab/pertuzumab (HP) in patients with stage 2 or 3 HER-2 positive breast cancer. All patients received additional anthracycline-based chemotherapy after surgery, regardless of response. Among arms, the THP combination was superior and demonstrated a pCR rate of 46%. Notably, even with the combination of trastuzumab and pertuzumab, without chemotherapy, 17% of patients experienced pCR, suggesting that for selected patients, treatment may potentially be de-escalated to exclude chemotherapy (20). To spare patients the potential long-term cardiac and myelotoxicity of anthracycline based regimens, the phase 2 TRYPHAENA trial examined the safety and efficacy of the anthracycline-free regimen TCHP (docetaxel, carboplatin, trastuzumab, pertuzumab) (21). This combination yielded a pCR rate of 66% with fewer declines in left ventricular ejection fraction compared to the anthracycline-based regimens. Further evidence supporting the use of an anthracycline-free regimen comes from the phase 3 TRAIN-2 trial demonstrating that a neoadjuvant platinum/taxane based regimen in combination with trastuzumab and pertuzumab provides equivalent 3-year EFS rates compared to a traditional anthracycline containing regimen (22). Overall, these pivotal neoadjuvant trials in HER-2 positive breast cancer show that between 50–80% of patients with HER-2 positive tumors will experience pCR following NACT with dual anti-HER-2 blockade and approximately 90% of patients who experience pCR will remain disease free 4 years after surgery (23).

Postoperative/adjuvant treatment escalation

Despite the significant improvements described above, between 20–50% of patients do not experience pCR. This patient population is at a higher risk for disease recurrence and death (HR with pCR, EFS: 0.39, 95% CI: 0.31–0.5; OS: 0.34, 95% CI: 0.24–0.47) (7) and thus warrants modification of the postoperative adjuvant therapy. The phase 3 KATHERINE trial randomized 1,486 HER-2 positive patients with residual disease following NACT and trastuzumab (approximately 18% in each arm received pertuzumab as well) to either standard adjuvant trastuzumab or T-DM1 [an antibody drug conjugate of trastuzumab (T) and the cytotoxic agent emtansine (DM1)] to complete 1 year of treatment. Patients receiving T-DM1 experienced a significant reduction in 3-year invasive disease-free survival (iDFS) (88.3% *vs.* 77%, P<0.001) (11). Given the results of this trial, neoadjuvant treatment in HER-2 positive breast cancer is now indicated not only to improve surgical outcomes and provide prognostic information, but also to predict a benefit for switching treatment from trastuzumab to T-DM1 in the postoperative setting. While the seminal neoadjuvant trials included only patients with stage 2 or 3 breast cancer the KATHERINE trial also included a small number of patients with stage 1 disease, suggesting a potential benefit of neoadjuvant treatment in this population as well. In the final efficacy results of the ExteNET trial which examined the role of 1 year of adjuvant treatment with the pan-HER tyrosine kinase inhibitor neratinib after one year of trastuzumab; among

Table 2 Narrative review search methods

Items	Specification
Date of search	July 2021 repeated March 2022 for updated data
Databases and other sources searched	PubMed, Cochrane Review, Clinical Trials.gov
Search terms used	Neoadjuvant chemotherapy and breast cancer
Timeframe	From July 1997 to February 2022
Inclusion and exclusion criteria	English only
Selection process	Selection conducted by all authors together
Additional considerations	A manual review of bibliographies identified additional relevant studies; newly published data was updated during the manuscript writing process

295 HR positive patients with residual disease post-NACT, one year of neratinib resulted in a 9.1% improvement in 8-year OS (91.3% *vs.* 82.2%, P=0.031) (24). These results are yet another example of how a HER-2 targeted agent can be personally tailored to improve patient outcomes based on their response to neoadjuvant treatment.

De-escalating treatment

As described, some patients have excellent responses to anti-HER-2 antibodies with single agent chemotherapy or without chemotherapy altogether, setting the stage for potential strategies for de-escalation of toxic chemotherapy in the neoadjuvant setting. The patient sub-groups that benefit from de-escalation still need to be defined (see biomarker discussion below). The ongoing Compass and Decrescendo trials are examining whether single agent taxane plus dual HER-2 inhibition with THP given for 4 cycles will be sufficient in patients who experience pCR (25,26). Patients with residual disease at surgery will receive adjuvant T-DM1 ± additional chemotherapy per investigator's choice. The KRISTINE trial which randomized 444 patients with stage 2–3 HER-2 positive breast cancer to 6 cycles of neoadjuvant T-DM1 with pertuzumab or TCHP showed inferior pCR rates and increased rates of locoregional progression before surgery with T-DM1 (27). With the results of this trial, the use of T-DM1 in the neoadjuvant setting has not been incorporated into standard clinical practice.

Biomarkers for response

De-escalation strategies should optimally rely on biomarkers for response to the targeted treatment. One possible biomarker is HR negativity as it is consistently correlated with superior pCR rates in HER-2 positive breast cancer (*Figure 1*). For example, in NeoSphere patients with HR negative disease treated with THP or the chemotherapy free HP combination had pCR rates of 63% and 27% respectively (20). In TRYPHAENA, HR negative patients receiving TCHP had a pCR rate of 83% compared to 50% among those with HR positive tumors (12). Lastly, in the phase 2 West German Study Group (WSG) ADAPT trial HER-2 positive HR negative patients were randomized to trastuzumab with pertuzumab ± paclitaxel. For the 42 patients receiving paclitaxel with trastuzumab and pertuzumab the pCR rate was 90.5% (28). Another potential predictor of response to anti-HER-2 treatment is intratumoral HER-2 heterogeneity. Filho *et al.* explored the role of intratumoral HER-2 heterogeneity in a single arm phase 2 trial of neoadjuvant T-DM1 with pertuzumab (29). Patients were biopsied in 2 different areas of the tumor with 3 cores taken from each area. Intratumoral HER-2 heterogeneity was defined as at least one of the six cores demonstrating either HER-2 positivity by flourescence in situ hybridization (FISH) in >5% and <50% of tumor cells or an area of tumor that tested HER-2 negative. Among 164 patients enrolled, none of the patients with HER-2 heterogenous tumors experienced pCR, suggesting that these patients may not be appropriate candidates for omission of chemotherapy. Molecular subtyping may also provide additional predictive information; in the phase 2 PAMELA trial 151 patients with HER-2 positive stage 1–3 breast cancer were treated with dual anti HER-2 blockade using lapatinib and trastuzumab for 18 weeks and the association between molecular subtype as defined by the PAM50 assay and pCR was evaluated (30). In this study 101/151 (67%) of the HER-2 positive patients were of the HER-2 enriched subtype. Notably 41% of these had pCR at surgery while 10% of the

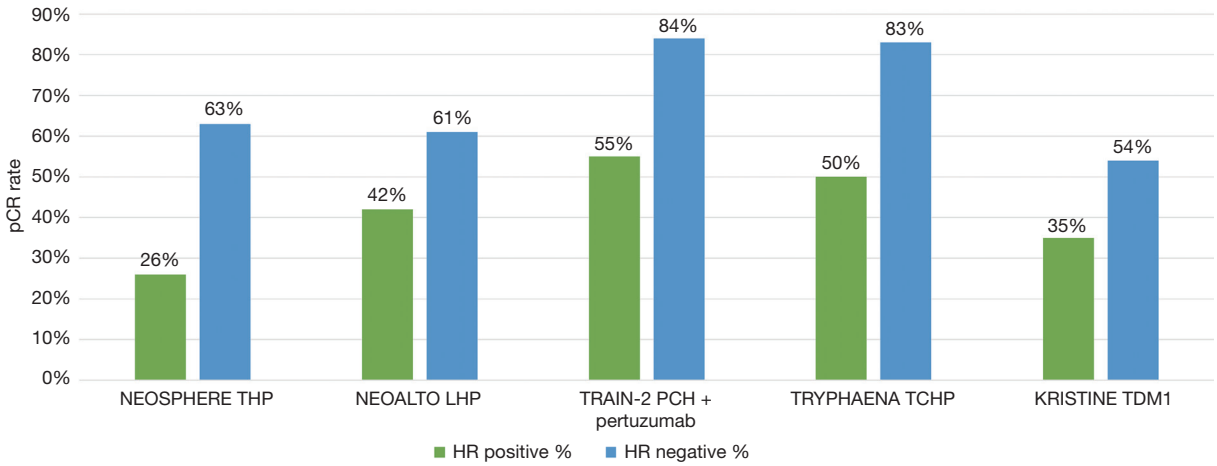

Figure 1 pCR rates in major trials of neoadjuvant dual HER2 inhibition by HR status. THP, docetaxel, trastuzumab, pertuzumab; LHP, lapatinib, trastuzumab, pertuzumab; PCH, paclitaxel, carboplatin, trastuzumab; TCHP, docetaxel, carboplatin, trastuzumab, pertuzumab; TDM-1, trastuzumab emtansine; HR, hormone receptor; pCR, pathological complete response.

non-HER-2 enriched tumors showed a pCR.

While these biomarkers are promising, until large randomized trials provide definitive evidence that certain populations can be spared multiagent chemotherapy without compromising long term outcomes, patients with HER-2 positive breast cancer undergoing neoadjuvant treatment should receive standard anthracycline based or platinum/taxane based chemotherapy combined with dual anti HER-2 inhibition with trastuzumab and pertuzumab (15).

Triple negative breast cancer (TNBC)

HR negative and HER-2 negative breast cancer known as TNBC composes approximately 15% of all cases of breast cancer, is more commonly diagnosed in women younger than 40 years and is considered to be more aggressive with worse prognosis (31,32). NACT may be offered to all chemotherapy eligible TNBC patients with tumors above 2 cm or positive lymph nodes, regardless of BCS eligibility (15). A pCR following NACT is of particular significance in TNBC as the association between long-term outcomes is strongest in this patient population (HR for EFS with pCR 0.24, 95% CI: 0.18–0.33) (7).

Historically anthracycline/taxane based regimens have been preferred in the treatment of TNBC (32). In the adjuvant setting in the combined analysis of the Anthracycline in Breast Cancer (ABC) trials the anthracycline-free regimen of docetaxel and cyclophosphamide (TC) was found to be inferior to standard anthracycline/taxane based chemotherapy, particularly for patients with TNBC or positive lymph nodes, reinforcing the continued role of anthracyclines in TNBC (33). In contrast in the WSG Plan B study adjuvant TC was found to be noninferior to a standard anthracycline/taxane regimen regardless of HR expression or lymph node status (34). In the neoadjuvant setting, there are some data suggesting that a taxane/platinum combination may provide similar pCR rates to the anthracycline/taxane based regimens. Sharma *et al.* (35) reported that pCR rate was 55% following NACT with docetaxel and carboplatin concluding that this regimen yields promising efficacy. Further support is seen in the phase 2 NeoSTOP trial where patients randomized to receive 6 cycles of docetaxel and carboplatin demonstrated an identical pCR rate as those that received 4 cycles of paclitaxel and carboplatin followed by 4 cycles of doxorubicin and cyclophosphamide (36). However, large neo-adjuvant trials comparing these regimens with EFS as an endpoint are lacking. Thus, anthracycline containing NACT regimens remain the standard in TNBC. For patients who are not eligible for anthracyclines due to a history of cardiac disease or major risk factors for cardiac toxicity the use of an anthracycline free regimen may be warranted.

The order and nature of the taxane

It appears that the sequence of treatment does not matter and the anthracyclines can either be followed or preceded by a taxane (37). In addition, there is no overwhelming evidence

that the nature of the taxane influences outcomes (38). In the adjuvant setting weekly or every 2 weeks solvent based paclitaxel appears to have the most efficacy (38,39) While nab-paclitaxel (nanoparticle albumin bound paclitaxel) has shown superiority to solvent-based paclitaxel in some studies, others have failed to show a significant difference. GeparSepto demonstrated improved pCR with nab-paclitaxel compared to paclitaxel in all breast cancer subtypes including TNBC (pCR entire cohort 38.4% *vs.* 29%, P=0.00065, TNBC 48% *vs.* 26%, P=0.00027) (40). This improvement in pCR translated to a significantly improved 4-year iDFS (41). In contrast, the ETNA trial which also compared these 2 taxanes in the neoadjuvant setting failed to show a significant difference in pCR rates (42).

Addition of carboplatin

The addition of carboplatin to standard anthracycline/taxane based NACT in TNBC is controversial. A meta-analysis of 9 randomized clinical trials including 2,109 patients found that the addition of platinum increased pCR rates significantly from 37% to 52.1% (P<0.001) with an increase in hematological toxicity (43). While effectively increasing pCR, its effect on long-term outcomes is uncertain. In GeparSixto the addition of carboplatin to the anthracycline/taxane backbone significantly improved pCR rates (53.2% *vs.* 36.9%, P=0.005) translating into an improvement in 3-year DFS (86% *vs.* 76%, P=0.022) (44,45). In contrast the addition of carboplatin to doxorubicin and paclitaxel in CALGB 40603 provided similar improvements in pCR yet failed to demonstrate an improvement in DFS (46,47). Notably, in GeparSixto patients with germline BRCA1/2 mutations did not experience improvements in pCR from the addition of carboplatin with exceptional pCR rates irrespective of carboplatin treatment (48). While current guidelines allow for the consideration of carboplatin as part of the neoadjuvant treatment of TNBC (15), the lack of definitive data demonstrating its effect on long term outcomes has prevented it from becoming a standard of care worldwide.

Addition of immune checkpoint inhibitors

Programmed cell death 1 (PD-1) is a transmembrane protein expressed on T cells, B cells, and NK cells. This protein binds to PD-1 ligand (PD-L1) and has an inhibitory effect, particularly on cytotoxic T cells (49). PD-L1 is expressed on the surface of multiple tissue types, including tumor cells and tumor infiltrating immune cells (50). Inhibition of the interaction between PD-1 to PD-L1 may restore the ability of T cells to identify and attack cancer cells (49). Various immune check point inhibitors (CPI) inhibiting PD-1 (pembrolizumab, nivolumab) or PD-L1 (atezolizumab, avelumab, durvalumab) have been approved for use in various tumor types. TNBC is considered the most immunogenic of all the breast cancer subtypes (51) and in the metastatic setting the combination of a CPI with chemotherapy has been shown to improve progression free survival (PFS) and OS in patients expressing PD-L1 on tumor cells or tumor infiltrating immune cells (52,53).

The beneficial role of the addition of CPI to NACT in TNBC is currently unfolding. The phase 3 KEYNOTE-522 trial examined the effect of adding pembrolizumab to an anthracycline/taxane based regimen including carboplatin in the neoadjuvant setting. At the first interim analysis the addition of pembrolizumab showed a 13.6% improvement in pCR (64.8% *vs.* 51.5%, P=0.00055) (54). A recently reported analysis of 3-year EFS demonstrated a significant improvement in favor of patients who received pembrolizumab (84.5% *vs.* 76.8%, P=0.00031) (55). In an exploratory subgroup analysis based on response to neoadjuvant treatment, patients who experienced pCR in both groups had excellent 3-year EFS outcomes [94.4% *vs.* 92.5%, P value not reported (NR)] while the patients who did not experience pCR appeared to derive a clinically significant benefit from the addition of pembrolizumab to the NACT regimen (3-year EFS: 67.4% *vs.* 56.8%, P value NR) (55). Based on these latest results the FDA has recently approved the use of pembrolizumab combined with NACT for neoadjuvant treatment of high risk TNBC. The phase 3 IMpassion031 trial examined the effect of adding atezolizumab to anthracycline/taxane based NACT without carboplatin. The addition of atezolizumab significantly increased pCR by 17% (58% *vs.* 41%, P=0.0044). EFS and OS results are immature (56). Smaller phase 2 trials have shown mixed results with CPI in the neoadjuvant setting. Both NeoTRIPaPDL1 which examined the addition atezolizumab to NACT and GeparNuevo which examined the addition of durvalumab to NACT did not demonstrate a statistically significant improvement in pCR (57,58), however the long term results of the GeparNuevo trial demonstrated a significant improvement in both DFS and OS despite the modest improvement in pCR (59). Thus, while pCR rates are highly correlated to prognosis after NACT treatment the correlation of pCR with neoadjuvant CPI treatment is not as clear. Importantly, CPI treatment may be associated with potentially severe and sometimes

long-term toxicity, particularly endocrinopathies requiring lifelong medication (60). As more long-term results become available in the next year, we expect that CPIs will be regularly incorporated into the neoadjuvant treatment regimens of TNBC.

Addition of poly-ADP-ribose polymerase (PARP) inhibitors

Up to 20% of patients with TNBC harbor a germline BRCA1/2 mutation (61). Carriers of deleterious BRCA1/2 mutations lose expression or function of BRCA1/2 proteins in cancer cells resulting in damage to the homologous DNA repair mechanism responsible for repairing double strand DNA breaks (62). The PARP are key players in repair of DNA single strand breaks (63). PARP inhibitors (PARPi) promote death of BRCA deficient cells by a "synthetic lethality" mechanism. These drugs prevent repair of single DNA strand breaks eventually causing accumulation of double strand breaks. In tumors without proper function of BRCA proteins these double strand breaks cannot be repaired causing death of the cancer cells (64).

PARPi are used in the treatment of metastatic breast cancer patients who carry a germline BRCA 1/2 mutation where they improved PFS (65,66) and possibly OS when used in first line (67). Recently, the phase 3 Olympia trial demonstrated that 1 year of adjuvant Olaparib significantly improves 3-year DFS (85.9% *vs.* 77.1%, P<0.001) in germline BRCA1/2 mutant breast cancer patients with at least stage 2 tumors that did not receive NACT or did not experience pCR following NACT (68).

The role of PARPi in the neoadjuvant setting is currently being explored. The adaptive phase 2 ISPY2 trial demonstrated that adding carboplatin and the PARPi veliparib to standard anthracycline/taxane NACT improved pCR compared to the standard anthracycline/taxane alone in patients with TNBC (51% *vs.* 26%, P value NR) (69). These results led to the phase 3 BrighTNEss trial which randomized 634 patients (15% germline BRCA 1/2 mutation) to either neoadjuvant paclitaxel plus carboplatin plus veliparib, paclitaxel plus carboplatin or paclitaxel alone. After receiving one of these three regimens all patients received 4 cycles of anthracycline based treatment. While both the carboplatin-veliparib combination and carboplatin monotherapy arms achieved increased pCR rates compared to paclitaxel alone, the addition of veliparib failed to improve pCR beyond that of carboplatin alone (70); suggesting that PARPi may not have a role in the neoadjuvant setting in patients already receiving a platinum agent. In a small study by Litton *et al.* (71) 10 out of 19 (53%) patients carrying germline BRCA 1/2 mutations who received single agent talazoparib for 6 months had a pCR. In the phase 2 NEOTALA study of 48 evaluable TNBC patients with germline BRCA1/2 mutations 45.8% demonstrated a pCR after 24 weeks of talazoparib treatment (72). These data are promising and various larger clinical trials using neoadjuvant PARPi as single agents or in combination with CPIs are planned. Use of neoadjuvant PARPi outside of clinical trials is currently not recommended.

The pCR rates for the major TNBC neoadjuvant trials are summarized in *Table 3*.

Post-operative treatment for patients not achieving pCR

The CREATE-X trial randomly assigned 910 patients with HER-2-negative residual invasive breast cancer after NACT to postsurgical treatment with capecitabine or placebo. Among patients with TNBC, the addition of capecitabine significantly improved DFS and OS (10). Similar to the KATHERINE trial in HER-2 positive patients (11) and Olympia in germline BRCA1/2 related breast cancer (68), CREATE-X demonstrated how postoperative treatment can be tailored to improve outcomes based on the response to NACT in TNBC.

HR positive breast cancer

NACT

While chemotherapy in HER-2 positive and TNBC is routinely used, the decision to administer NACT in HR positive breast cancer is more complex, as many patients are not expected to derive a significant survival benefit from chemotherapy (73). While it has been reported that following NACT over 70% of HR positive patients have a clinical and pathological response in the breast and up to 21.1% have been shown to have a complete pathological axillary response (74), it is still unclear which patients will be able to avoid mastectomy or the sequelae of an ALND (75) after NACT. The pCR rates are very low, with an expected rate of less than 10% in low grade tumors and less than 20% in high grade tumors (7). Moreover, the prognostic value of pCR in HR positive disease is questionable, especially in low grade luminal A like disease [defined clinically as high estrogen receptor (ER) and progesterone receptor (PR) levels, negative HER-2 and Ki-67 <15%] indicating a need for better pathologic response measures

Table 3 pCR rates in major neoadjuvant trials in TNBC

Study	Study design	pCR	Treatment arms	Number of TNBC patients	pCR	P value	DFS/EFS	P value
GeparSixto (44,45)	Phase II	ypT0pN0	P + Dox + Bev + Cb	158	53.2%	0.005	86.1%	0.0224
			P + Dox + Bev	157	36.9%		75.8%	
CALGB 40603 (46,47)	Phase II	ypT0/is	P + Cb → ddAC ± Bev	221	60%	0.0018	NR	
			P → ddAC ± Bev	212	46%		NR	
Keynote 522 (54,55)	Phase III	ypT0/TisypN0	Pembrolizumab + P + Cb → AC	784	64.8%	<0.001	84.3%	0.0003
			Placebo + P + Cb → AC	390	51.2%		76.2%	
IMpassion031 (56)	Phase III	ypT0/is ypN0	Atezolizumab + NabP → AC	165	58%	0.0044	Immature	
			Placebo + NabP → AC	168	41%		Immature	
GeparNuevo (58,59)	Phase II	ypT0 ypN0	Durvalumab + NabP → EC + durvalumab	88	53.4%	0.224	85.6%	0.0398
			Placebo + NabP → EC + placebo	86	44.2%		77.2%	
BrighTNess (70)	Phase III	ypT0pN0	P + Cb + veliparib → AC	316	53%	0.36*	78%	
			P + Cb + placebo → AC	160	58%	<0.001**	79%	
			P + placebo → AC	158	31%		69%	0.02

*, P + Cb + veliparib *vs.* P + Cb; **, P + Cb + veliparib *vs.* P + placebo. pCR, pathological complete response; TNBC, triple negative breast cancer; DFS, disease-free survival; EFS, event free survival; P, paclitaxel; Dox, doxorubicin; Bev, bevaciumab; Cb, carboplatin; dd, dose dense; AC, adriamycin-cyclophosphamide; NR, not reported; NabP, nabpaclitaxel; EC, epirubicin + cyclophosphamide.

of neoadjuvant treatment in this patient population (76). Efforts have been made to define HR positive subgroups that will derive benefit from NACT. Gene expression profiles such as Oncotype Dx and MammaPrint, commonly used to support adjuvant chemotherapy decision-making in HR positive breast cancer are being explored in the neoadjuvant setting. There is a growing amount of evidence showing the concordance of gene expression profiles derived from preoperative core needle biopsies to surgical specimens (77,78) and their ability to potentially predict response to neoadjuvant systemic therapies (*Tables 4-6*) (79-94). For instance, in the NACT portion of the WSG ADAPT trial, Oncotype Dx recurrence scores (RS) performed on presurgical biopsies were predictive of pCR (82). While pCR rates were low overall, patients with an RS >25 had a significantly higher pCR rate than patients with an RS ≤25 (16.1% *vs.* 7.2%, P=0.006). This difference was most evident amongst premenopausal patients (17.2% *vs.* 4.8%, P=0.03) while the difference among postmenopausal patients was not significant (15.2% *vs.* 12.2%, P=0.8). Therefore, if a patient has a preoperative genomic risk score predicting long term benefits from chemotherapy it may be reasonable to administer NACT particularly if tumor or axillary downstaging is required to improve surgical outcomes. Notably, while gene expression profiles may be used in the clinic to guide clinical decision making regarding NACT (95) current guidelines do not recommend their routine use in this setting (15).

Neoadjuvant endocrine treatment (NET)

For post-menopausal HR positive patients in need of surgical downstaging who are either not candidates or are not predicted to benefit from chemotherapy, another option is NET. Currently, due to a limited amount of data in premenopausal patients, NET should not be regularly recommended in this patient population. Although pCR is rarely achieved with NET, clinical response rate (CRR) and BCS rates, while varying between trials, appear to be comparable to NACT and with less toxicity (96).

The pivotal trials in NET have demonstrated the superiority of aromatase inhibitors (AIs) over tamoxifen

Table 4 Neoadjuvant oncotype studies with 11 and 25 RS cutoffs

Author	Gene expression profile	Study type	Patient population	Number of patients	Treatment	Endpoints	Low risk <11	Low risk <25	Intermediate risk 11–25	High risk >25	P value
Morales Murillo *et al.* 2021 (79)	Oncotype Dx	Prospective	HR pos HER2 neg	60	NACT NS	RCB 0/1	NA		PostMp: 6.7%, PreMp: 0%, RS (11–20)	PostMp: 52.6%, PreMp: 42.9%, RS >20	NA
Bear *et al.* 2017 (80)	Oncotype Dx	Prospective	HR pos HER2 neg	64	Anthracycline/ taxane NACT or ET	CRR, BCS, pCR	ET: 83.3%, 75%, 0%		ET: 50%, 72.2%, 0%, CT: 72.7%, 63.6%, 0%	CT: 92.9%, 57.1%, 14.3%	0.049, NA, NA
Sella *et al.* 2021 (81)	Oncotype Dx	Retrospective	HR pos HER2 neg age <40	76	Anthracycline/ taxane NACT	pCR		5%		21%	0.09
Kuemmel *et al.* 2020 (82)	Oncotype Dx	Prospective	HR pos HER2 neg	864	Anthracycline/ taxane NACT	pCR		7%, PostMp: 12.2%, PreMp: 4.8%		16%, PostMp: 15.2%, PreMp: 17.2%	0.006, 0.8, 0.003
Thekkekara *et al.* 2019 (83)	Oncotype Dx	Retrospective	HR pos HER2 neg	110	NACT NS	CRR, pCR		32.5%, 0%		81.4%, 16%	NA, NA

RS, recurrence score; HR, hormone receptor; pos, positive; neg, negative; NACT, neoadjuvant chemotherapy; NS, nonsignificant; RCB, residual cancer burden; NA, not available; PostMp, postmenopausal; PreMp, premenopausal; ET, endocrine therapy; CRR, clinical response rate; BCS, breast conserving surgery; pCR, pathological complete response; CT, chemotherapy.

in terms of response rates and surgical outcomes. P024 randomized 337 postmenopausal BCS-ineligible patients to 4 months of NET with letrozole or tamoxifen (97) with superior CRRs (55% *vs.* 36%, P<0.001) and BCS rates (45% *vs.* 35%, P=0.022) associated with the letrozole. In PROACT, 451 postmenopausal patients were randomized to 12 weeks of preoperative anastrozole or tamoxifen (98) with concomitant chemotherapy allowed. Among the 262 patients treated with NET alone and ineligible for upfront BCS the CRR was significantly superior with anastrozole (49% *vs.* 36%, P=0.04). There were no significant differences in BCS between the two groups (38% *vs.* 30%, P=0.11). PROACT also provided data on axillary downstaging. Amongst the 201 patients with node positive disease, 43.4% of patients in the letrozole group and 38.5% of patients in the tamoxifen group experienced clinical downstaging of the axilla. To date there are limited prospective data regarding the approach to the axilla following NET with retrospective data indicating between a 10–15% axillary pCR rate (99). The IMPACT trial randomized 330 postmenopausal patients to 12 weeks of preoperative anastrozole, tamoxifen or the combination (100). CRRs were similar between groups and amongst the 124 patients initially ineligible for BCS, 44% of those treated with anastrozole had BCS compared with 31% receiving tamoxifen (P=0.23). Additionally, the rate of patients deemed eligible by their surgeons for BCS were significantly higher following anastrozole than tamoxifen or the combination (46%, 22% and 26% respectively, P=0.03). This study also provided early biomarker data as higher levels of ER were shown to correlate with response. Additionally, tumor cell proliferation as measured by a decrease in Ki-67 levels 2 weeks following treatment was significantly improved in the anastrozole group (101) and was associated with improved recurrence free survival (102).

NACT vs. NET

The largest trial comparing NACT to NET randomized 239 postmenopausal women to NET with an AI (exemestane or anastrozole) or to NACT with doxorubicin and paclitaxel (103). CRRs were 64% in both the NET and chemotherapy arms, pCR rates were low in both arms (3% and 6% respectively) and there was a non-statistically significant numerical difference in BCS rates in favor of NET (33% *vs.* 24%, P=0.058). Kim *et al.* (104) randomized

Table 5 Neoadjuvant oncotype studies with 18 and 30 RS cutoffs

Author	Gene expression profile	Study type	Patient population	Number of patients	Treatment	End points	Low risk <18	Intermediate risk 18–30	High risk >30	P value
Pardo *et al.* 2021 (84)	Oncotype Dx	Retrospective	HR pos HER2 neg	158	NACT not specified	Axillary pCR	10.7%	9.7%	27.5%	0.0268
Iwata *et al.* 2019 (85)	Oncotype Dx	Prospective	HR pos HER2 neg	295	Letrozole	CRR, BCS	54%, 79%	42%, NA	22%, 60%	<0.001, 0.009
Pivot *et al.* 2015 (86)	Oncotype Dx	Prospective	HR pos HER2 neg	81	Anthracycline/ taxane NACT	pCR	0%	6.2%	8.6%	0.004
Yardley *et al.* 2015 (87)	Oncotype Dx	Prospective	HER2 neg	108	Ixabepilone/ cyclophosphamide	pCR	0%	0%	17% (HR neg) 31% (HR pos)	0.002
Ueno *et al.* 2014 (88)	Oncotype Dx	Prospective	HR pos	64	Exemestane	CRR	59.4%	58.8%	20%	0.015
Akashi-Tanaka *et al.* 2009 (89)	Oncotype Dx	Prospective	HR pos	43	Tamoxifen or anastrazole	CRR	64%	31%	31%	0.11
Chang *et al.* 2008 (90)	Oncotype Dx	Prospective	Locally advanced all subtypes	97	Docetaxel	CRR	0%	NA	21.4%	NA

RS, recurrence score; HR, hormone receptor; pos, positive; neg, negative; NACT, neoadjuvant chemotherapy; pCR, pathological complete response; BCS, breast conserving surgery; CRR, clinical response rate; NA, not available.

Table 6 Additional neoadjuvant gene expression profile studies

Author	Gene expression profile	Study type	Patient population	Number of patients	Treatment	End points	Low risk	Intermediate risk	High risk	P value
Dubsky *et al.* 2020 (91)	Endopredict	Retrospective	HR pos HER2 neg	134	Anthracycline/ taxane NACT ± tecemotide	RCB 0/1	0%	NR	26.4%	0.112
Dubsky *et al.* 2020 (91)	Endopredict	Retrospective	HR pos HER2 neg	83	Letrozole ± tecemotide	RCB 0/1	27.3%	NR	7.7%	
Whitworth *et al.* 2017 (92)	Mammaprint/ Blueprint	Prospective	HR pos HER2 neg	474	Anthracycline/ taxane NACT	pCR	2%	NR	13%	0.001
Mathieu *et al.* 2012 (93)	BCI	Retrospective	All subtypes	150	Anthracycline/ taxane NACT	pCR, BCS	1.6%, 14%	21%, 46%	29%, 44%	0.0001, 0.0002
Straver *et al.* 2010 (94)	Mammaprint	Retrospective	All subtypes	167	Anthracycline/ taxane NACT ± trastuzumab	pCR	0%	NR	20%	0.015

HR, hormone receptor; pos, positive; neg, negative; NACT, neoadjuvant chemotherapy; RCB, residual cancer burden; NR, not reported; pCR, pathological complete response; BCI, breast cancer index; BCS, breast conserving surgery.

187 premenopausal women to anthracycline/taxane based NACT or NET with goserelin and tamoxifen with the primary endpoint of CRR at 24 weeks. While there were no differences in BCS (13.8% *vs.* 11.5%, P=0.531), patients receiving NACT had a significantly better CRR (84% *vs.* 71%, P=0.046). In GEICAM/2006-03, 95 patients, 51 of

which were premenopausal, were randomized to NET with exemestane (+ goserelin if premenopausal) or NACT (105). Similarly, premenopausal women experienced significantly greater CRR to NACT (75% *vs.* 44%, P=0.027), while no difference was seen among post-menopausal women (57% *vs.* 52%, P=0.78). The pCR rates were exceptionally low in both groups (NACT: 2%, NET: 0%) and there were no differences in BCS or axillary nodal status after surgery.

Potential biomarkers of response to NET

With pCR being a rare occurrence, data from the earlier NET trials supported the development of a distinct surrogate pathologic marker of response to NET known as preoperative endocrine prognostic index (PEPI) (106). This score was developed by analyzing post treatment factors associated with survival in P024 and independently validated in a cohort of patients from IMPACT. PEPI is based on the post-NET surgical specimen and calculated as the sum of points given to 4 categories: tumor size, nodal status, Ki-67 level, and ER expression. Patients with a PEPI of 0 (pT0/1, N0, Ki67 <2.7%, and positive ER), have very favorable outcomes without chemotherapy. In ACOSOG Z1031 377 postmenopausal patients were randomized to 16–18 weeks of NET with an AI (letrozole, anastrozole or exemestane) (107) with comparable CRR and BCS rates between arms. The PEPI score was a secondary endpoint and tumors were subtyped by a PAM-50 analysis. CRRs were 62.9%, 74.8% and 69.1% for exemestane, letrozole, and anastrozole, respectively. In patients designated as requiring a mastectomy before treatment 51% were subsequently able to undergo BCS, and 83% of patients who were considered marginal for breast conservation underwent BCS. There was no difference between CRR or BCS rates between luminal A and luminal B cancers, however significantly more patients with luminal A disease had a PEPI score of 0 (27.1% *vs.* 10.7%, P=0.004). At a median follow-up of 5.5 years, of 421 patients from Z1031 eligible for long-term analysis, 119 (25.9%) had a PEPI 0 response and only 4 (3.3%) recurrences were identified in this group as opposed to 49 (14.4%) in patients with a PEPI score >0 (108).

NET in premenopausal women

As discussed, 2 studies comparing NACT to NET showed a significantly greater CRR in premenopausal patients receiving NACT. The phase 3 STAGE trial randomized 197 premenopausal patients to 24 weeks of preoperative goserelin with anastrozole or tamoxifen (109). Patients in the anastrozole group had a CRR of 70.4% *vs.* 50.5% in the tamoxifen group (P=0.004). Despite this promising trial, data is still limited on the role of NET in this patient population and more studies are needed to properly identify premenopausal patients who are most likely to benefit from this treatment approach.

The main findings of the major NET trials are summarized in *Table 7*.

NET combined with CDK4/6 inhibitors

CDK4/6 inhibitors (abemaciclib, palbociclib, ribociclib) in combination with endocrine therapy have become a standard of care in metastatic HR positive breast cancer (110). Their role in the neoadjuvant/adjuvant setting is still under investigation. The NeoPAL study randomized 106 Prosigna defined luminal A or B stage 2 or 3 patients ineligible for BCS to either letrozole plus palbociclib or standard anthracycline and taxane based chemotherapy (111). The pCR rates were low in both arms (two patients in the palbociclib arm and three in the chemotherapy arm) and the CRRs and BCS rates were identical. The single arm NeoPalana trial (n=50) examined whether the addition of palbociclib to anastrozole increased the rate of complete cell cycle arrest (CCCA) defined as Ki67 <2.7% (112). CCCA was observed among 26% of patients following anastrozole as opposed to 87% after combined treatment (112). Similar improvements in CCCA were observed with abemaciclib in the neoMONARCH trial (113). Thus, while current data indicate that the addition of CDK4/6 inhibition may increase the antiproliferative effect of endocrine treatment and dramatically decrease Ki-67 expression, to date no study has shown an improvement in CRR or BCS rates which are the primary goal of NET. The optimal endpoint to neoadjuvant CDK4/6 trials and their effect on long term outcomes is also unclear. In the adjuvant setting, early results from the MonarchE study comparing adjuvant endocrine therapy with an AI with or without 2 years of abemaciclib in high risk patients showed a significant improvement in 2-year iDFS (114). In contrast two adjuvant trials using palbociclib failed to show an improvement in DFS (115,116). While promising, in the neoadjuvant setting these agents should currently only be used within a clinical trial.

Conclusions

Over the last two decades, we have come to understand

Table 7 Major NET trials

Trial	Year	Treatment arms	Patient population	Number of patients	CRR	BCS rate	P value (CRR, BCS rate)
Eiermann *et al.* (97)	2001	Letrozole *vs.* tamoxifen, 4 months	Post-menopausal, stage II/III, BCS ineligible	337	Letrozole =55%, tamoxifen =37%	Letrozole =45%, tamoxifen =35%	<0.001, 0.022
Cataliotti *et al.* (98)	2006	Anastrozole *vs.* tamoxifen ± CT, 12 weeks	Postmenopausal, tumor size >3 cm	262 (ET alone)	Anastrozole =49%, tamoxifen =36%	Anastrozole =38%, tamoxifen =30%	0.04, 0.11
Smith *et al.* (100)	2005	Anastrozole, tamoxifen or both, 3 months	Postmenopausal	330	Anastrozole =37%, tamoxifen =36%, combination =39%	Anastrozole =44%, tamoxifen =31%	0.87, 0.23
Semizaglov *et al.* (103)	2007	A + T *vs.* exemestane or anastrozole, 3 months	Post-menopausal, stage II/III	239	ET =64.5%, CT =63.6%	ET =33%, CT =24%	>0.5, 0.058
Kim *et al.* (104)	2020	AC-T *vs.* goserelin + tamoxifen, 24 weeks	Pre-menopausal, stage II/III	187	84%, 71%	13.8%, 11.5%	0.046, 0.531
Alba *et al.* (105)	2012	AC-T *vs.* exemestane ± goserelin, 24 weeks	Pre/post-menopausal, stage II/III	95	Premenopausal: ET =44%, CT =75%; postmenopausal: ET =52%, CT =57%	ET =56%, CT =47%	0.78, 0.2369
Ellis *et al.* (107)	2011	Anastrozole, letrozole, exemestane	Postmenopausal, stage II/III	377	Anastrozole =69%, letrozole =75%, exemestane =63%	Anastrozole =77%, letrozole =61%, exemestane =68%, 51% BCS ineligible underwent BCS in entire cohort	NA, NA
Masuda *et al.* (109)	2012	Goserelin + tamoxifen or anastrozole, 24 weeks	Premenopausal	197	Anastrozole =70%, tamoxifen =50%	Anastrozole =86%, tamoxifen =68%	0.004, NA

NET, neoadjuvant endocrine treatment; CRR, clinical response rate; BCS, breast conserving surgery; CT, chemotherapy; ET, endocrine therapy; A, doxorubicin; T, taxane; C, cyclophosphamide; NA, not available.

that neoadjuvant systemic therapy is as safe and effective as adjuvant therapy (2). In patients with operable breast cancer neoadjuvant therapy can be considered for all patients determined upfront to require systemic adjuvant treatment. If given preoperatively this treatment may improve surgical outcomes. In patients with TN and HER-2 positive tumors, neoadjuvant systemic therapy should also be considered not only for the improvement of surgical outcomes, but also for the prognostic and predictive information the response to treatment will provide. Neoadjuvant therapy also offers a window of opportunity to research novel biomarkers allowing for a more tailored approach to patient care. At present, the role of neoadjuvant systemic therapy in early breast cancer in both contemporary clinical practice and the research setting is continuing to develop with the likelihood that its applications will continue to expand, further emphasizing the importance of multidisciplinary communication to provide the best outcomes for our patients.

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Footnote

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