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REVIEW

Addressing Residual Disease in HER2-Positive and Triple-Negative Breast Cancer: What Is Next?

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Abstract

Purpose of review To summarize the treatment strategies for patients with human epidermal growth factor receptor 2 (HER2)-positive disease and triple-negative breast cancer (TNBC) who have residual disease after preoperative systemic therapy.

Recent findings There has been a shift towards neoadjuvant systemic therapy for selected patients with HER2-positive and TNBC. Assessing the tumor's response to therapy provides prognostic information and allows individualization of the post-operative treatment for these patients based on the tumor response to neoadjuvant therapy. Patients with TNBC with residual disease after neoadjuvant therapy can be treated with pembrolizumab, capecitabine, or olaparib. Those with HER2-positive disease are treated with adjuvant trastuzumab emtansine.

Summary The treatment of early breast cancer has evolved significantly, and patient outcomes continue to improve. As better treatments are developed, we will need biomarkers to determine which patients may benefit from certain therapies to continue to improve outcomes by right-sizing treatments and limiting toxicities.

Keywords Breast cancer · Neoadjuvant therapy · Adjuvant therapy · Olaparib · Pembrolizumab · Capecitabine · T-DM1

Introduction

Breast cancer is the most common malignancy and the second most common cause of cancer-related mortality in the USA [1]. The majority (approximately 65%) of patients in the USA present with localized disease [2]. The cornerstone of systemic treatment for breast cancer is chemotherapy, targeted therapy, and immunotherapy. Treatment decisions and prognosis are based on the hormone receptor (HR) status and human epidermal growth factor receptor 2 (HER2) overexpression or amplification. Approximately 70% of breast cancers express HR (estrogen and/or progesterone receptors), while around 15% overexpress HER2 (from which half also express HR). The remaining 15% do not express HR or HER2, and this breast cancer subtype is known as triple-negative breast cancer (TNBC) [2].

Systemic treatment for early breast cancer can be administered before or after definitive surgery. A meta-analysis from the Early Breast Cancer Trialists' Collaborative Group (EBCTCG) showed no difference in breast cancer mortality for patients receiving preoperative (neoadjuvant) or postoperative (adjuvant) chemotherapy [3]. However, this analysis did not incorporate some of the modern therapies that are now part of our armamentarium. Based on these findings, until recently, there was no consensus about the optimal treatment sequencing for patients with breast cancer, and decisions were made based on the tumor size, feasibility for surgery, and patient preference. In recent years, there has been a shift towards neoadjuvant systemic therapy for patients with HER2-positive disease and TNBC and tumors larger than 2 cm or with nodal involvement. The main reason for this change is to allow the clinician to assess the tumor response to therapy, which confers prognostic information [4••]. And perhaps more importantly, it allows individualization of the postoperative treatment for these patients based on the tumor response to neoadjuvant therapy [5••,

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6••]. Several studies have shown that treatment intensification for patients with residual disease after neoadjuvant therapy can lead to improved long-term outcomes. Examples include capecitabine for TNBC and trastuzumab-emtansine (T-DM1) in those with HER2-positive disease, both discussed in detail in this review [5••, 6••].

In this narrative review, we summarize the evidence of treatment of early breast cancer, particularly for patients with HER2-positive disease and TNBC who have residual disease after neoadjuvant systemic therapy.

Assessing Response to Therapy and Prognosis Beyond Receptor Status

Pathological complete response (pCR) is defined as the absence of invasive breast cancer in the breast and/or local lymph nodes (with some definitions including ductal carcinoma in situ) and has shown to correlate with long-term outcomes for patients with early HER2-positive disease and TNBC [4••]. A pooled analysis of 11,955 patients enrolled in 12 different trials revealed a strong association between pCR, event-free survival (EFS), and overall survival (OS) (EFS: HR 0.24, 95% CI 0.18–0.33; OS: HR 0.16, 95% CI 0.11–0.25) in patients with TNBC. In those patients with HER2-positive tumors who received trastuzumab, there was also a strong association between pCR and long-term outcomes (EFS: HR 0.15, 95% CI 0.09–0.27; OS: HR 0.08, 95% CI 0.03–0.22).

Based on the pooled analysis by Cortazar et al. [4••], patients with TNBC tumors larger than 2 cm and/or with lymph node involvement are often treated with neoadjuvant treatment as it has been well established that assessing response and modifying treatment can lead to improved outcomes [4••]. Of note, since the publication of this pooled analysis, immunotherapy has been approved in combination with chemotherapy for patients with high-risk TNBC in the neoadjuvant setting, and, at the moment, it is unclear if pCR is the optimal surrogate of long-term outcomes for patients treated with immune checkpoint inhibitors [4••, 7••]

Similarly, in patients with HER2-positive tumors, those who achieve a pCR with trastuzumab with/or without pertuzumab have better EFS [4••, 8]. Therefore, patients with tumors larger than 2 cm and/or with lymph node involvement are recommended to be treated with neoadjuvant chemotherapy in combination with HER2-directed monoclonal antibodies with the goal to assess response to treatment and to be able to tailor treatment in the post-neoadjuvant setting.

In addition to pCR, other potential prognostic markers have been studied in this setting. The residual cancer burden (RCB) quantifies the amount of residual disease after neoadjuvant therapy [9]. RCB is calculated based on the size of the tumor bed, overall cellularity, area of in situ disease, number of lymph nodes affected, and diameter of lymph node metastases and leads to a continuous score that can be divided into 4 classes (0 to III), with RCB 0 corresponding to pCR. RCB has been shown to be a good surrogate for long-term outcomes in patients treated with neoadjuvant chemotherapy irrespective of HR status and for patients with TNBC treated with chemoimmunotherapy [9, 10•]. Even though RCB appears to be a good correlative marker of long-term outcomes for different breast cancer subtypes [11], including distant recurrence-free survival, the trials that have led to approvals in the post-neoadjuvant setting have focused primarily on pCR.

Triple-Negative Breast Cancer

Current Adjuvant Treatment Options for Patients with TNBC and Residual Disease After Neoadjuvant Therapy

The standard neoadjuvant treatments for patients with TNBC with tumors 2 cm or larger or with lymph node involvement include a combination regimen of an anthracycline, cyclophosphamide, carboplatin, paclitaxel, and pembrolizumab per the KEYNOTE-522 trial [12•]. The addition of pembrolizumab led to an improvement in pCR of 13.6%, with a pCR of 64.8% in the chemoimmunotherapy arm, and 51.2% in the chemotherapy-placebo arm, although the benefit appeared to be smaller (8%) after more patients were enrolled in the study and completed neoadjuvant therapy. After definitive local therapy (surgery +/− radiation), patients received up to 9 cycles of pembrolizumab in this study, irrespective of response to therapy, nodal status, or programmed cell death ligand 1 (PD-L1) expression. In this study, the addition of immunotherapy led to an improvement in EFS at 39.1 months (15.7 vs 23.8% [HR 0.63, 95% CI 0.48–0.82, $p < 0.001$]). An updated analysis with a 63.1-month follow-up revealed an EFS of 81.3% in the pembrolizumab arm vs 72.3% in the chemotherapy arm (HR 0.63, 95% CI 0.49–0.81) [13]. This analysis also revealed that pembrolizumab led to improved outcomes in those with node-negative disease with an EFS of 86.3% vs 77.8% (HR 0.56, 95% CI 0.38–0.84) and in those with cT2N0 disease with an EFS of 87.8 vs 77.9 (HR 0.49, 95% CI 0.31–0.78). In KEYNOTE-522, all patients received post-neoadjuvant pembrolizumab monotherapy irrespective of pCR; the actual benefit of pembrolizumab in the adjuvant setting for those who achieve a pCR is unclear. In this study, most high-grade adverse events occurred during the neoadjuvant phase, and for those who received immunotherapy, there was a higher grade of diarrhea (30.4% vs 25.2%), rash (25% vs 17%), hypothyroidism (15.1% vs 5.7%), and other

immune-mediated toxicities including hyperthyroidism, adrenal insufficiency, and pneumonitis.

Prior to the approval of pembrolizumab in this setting, the standard treatment for patients with high-risk TNBC was an anthracycline and taxane-containing regimen (with or without carboplatin) in the neoadjuvant setting followed by capecitabine per the CREATE-X trial for patients with residual disease [5••, 14•]. CREATE-X was a phase 3 trial in which 910 patients with HER2-negative early breast cancer (around 70% HR-positive and 30% TNBC) with any residual disease after neoadjuvant therapy were randomized to capecitabine (1250 mg/m2 twice a day for days 1 to 14 every three weeks for 6 to 8 cycles) or observation [5••]. This study revealed that the 5-year disease-free survival (DFS) was higher in the treatment arm vs the observation arm (74.1 vs 67.6%, HR 0.70, 95% CI 0.53–0.92, $p = 0.01$), and the OS was greater in the capecitabine group (89.2 vs 83.6%, HR 0.59, 95% CI 0.39–0.90, $p = 0.01$). The benefit was greater in patients with TNBC, and in this group, the DFS was 69.8 vs 56.1% and OS was 78.8 vs 70.3%. In terms of toxicities, capecitabine compared to observation was more often associated with hand foot syndrome (11.1% with grade 3–4 vs 0), neutropenia (6.3% with grade 3–4 vs 0), diarrhea (2.9% with grade 3–4 vs 0), leukopenia (1.6% with grade 3–4 vs 0.2%), and fatigue (1.1% with grade 3–4 vs 0). Notably, in the ECOG-ACRIN EA1131 phase 3 trial that compared capecitabine to platinum in patients with TNBC and at least 1 cm of residual disease after neoadjuvant therapy [15••], the invasive DFS (iDFS) was 42% with platinum and 49% with capecitabine at a median follow up of 3 years. In this study, platinum therapy did not meet non-inferiority criteria, so the trial was discontinued. Based on these findings, until the approval of pembrolizumab by the U.S. Food and Drug Administration (FDA) for early-stage TNBC in 2021, the standard of care for patients with residual disease after neoadjuvant therapy was capecitabine. An important question remains on how to reconcile the results from CREATE-X and KEYNOTE-522 when deciding the optimal management of patients with TNBC and residual disease after neoadjuvant chemotherapy. The combination of capecitabine and immunotherapy has been studied, and it seems to be safe; however, the efficacy of this combination in patients with TNBC and residual disease is unknown. A small ($n = 30$) phase 2 study assessed the safety of this combination in patients with heavily pretreated advanced HER2-negative breast cancer and revealed the expected safety profile of these agents [16]. The mentioned OXEL trial also assessed the safety of the combination [17•]. Given that the combination appears to be safe and patients with residual disease have poor outcomes, the combination could be considered in clinical practice. However, shared decision-making is required as there is a risk of toxicity, and it is unknown if combining these agents leads to improved long-term outcomes.

Around 5% of patients with breast cancer carry a germline pathogenic variant in the homologous recombination repair genes *BRCA1* or *BRCA2* [18]. Poly(adenosine disphophate-ribose) polymerase (PARP) inhibitors, such as olaparib, have shown efficacy in killing cells with a homologous recombination deficiency and have been approved for the treatment of several malignancies, including metastatic HER2-negative breast cancer [19, 20]. OlympiA was a phase 3 trial in which 1836 patients with germline pathogenic or likely pathogenic *BRCA1/2* variants and high risk HER2-negative breast cancer were randomized to receive 1 year treatment of olaparib (300 mg twice daily) or placebo [21••]. In this study, over 70% of patients carried a *BRCA1* variant, half received adjuvant chemotherapy, over 80% had TNBC, and the remainder had HR-positive disease. Patients were eligible after neoadjuvant therapy if they did not achieve a pCR and had TNBC or if they had HR-positive breast cancer, did not achieved pCR and had other high-risk characteristics based on CPS-EG score [22]. Patients were also eligible if they received adjuvant therapy for TNBC and had tumors larger than 2 cm or with lymph node involvement or HR-positive breast cancer with 4 or more lymph nodes involved. The 3-year iDFS was 86.1% in the olaparib arm and 77.3% in the placebo arm, the OS was 92% in the olaparib arm and 89.1% in the placebo arm (HR 0.68, 95% CI 0.47–0.97, $p = 0.009$). Patients treated with olaparib reported higher rates of nausea (56.9 vs 23.3%), vomiting (22.6 vs 8.2%), fatigue (40 vs 27.1%), anemia (23.5 vs 3.9%), and neutropenia (16 vs 6.5%). Based on OlympiA, olaparib was approved by the U.S. FDA in March of 2022 for the adjuvant treatment of patients with germline BRCA-mutated HER2-negative high-risk early breast cancer. Since then, national guidelines have expanded to offer germline testing to patients with BRCA-associated high-risk HER2-negative breast cancer, irrespective of family history. For patients with TNBC and residual disease after neoadjuvant therapy who carry a germline pathogenic/likely pathogenic *BRCA1/2* mutation, one could consider olaparib according to the OlympiA study or combination therapy with olaparib and pembrolizumab. Several studies have shown that combining immunotherapy and PARP inhibitors appears to be safe. Preclinical studies have shown that they appear to have a synergistic effect [23, 24], although this was not confirmed in a randomized trial in the metastatic setting [25]. It is unknown if the combination in the early-stage setting leads to improved patient outcomes. In contrast, the combination of chemotherapy and PARP inhibitors has been associated with dose-limiting cytopenias in prior studies; therefore, this combination is not recommended outside of a clinical trial [24, 26, 27].

Figure 1 shows our current treatment algorithm for patients with TNBC and residual disease, a group of patients with historically poor prognosis that now have novel and promising treatment options available. Table 1 summarizes the trials. However, several questions remain and will be discussed in the next section.

Clinical Questions and Ongoing Trials

There are several questions about the best treatment regimen in the post-neoadjuvant setting. Should all patients receive adjuvant pembrolizumab irrespective of pCR? In KEYNOTE-522, patients with residual disease appeared to derive a greater benefit with adjuvant pembrolizumab; therefore, it is possible that patients with pCR could forgo additional treatment, decreasing the risk for adverse events and financial toxicities. Given that all patients in the study received adjuvant immunotherapy, it is not possible to assess if selected patients can forgo this part of the treatment, and therefore, our algorithm proposes to continue treatment per the study. This is an area of active research to continue to personalize the treatment of patients with early breast cancer. For example, in the OptimICE-pCR trial (NCT05812807), patients with pCR after neoadjuvant chemoimmunotherapy are being randomized to pembrolizumab per KEYNOTE-522 vs observation.

Another question in clinic that remains unanswered is whether patients will have better outcomes if we combine different treatments that were approved based on the KEYNOTE-522, CREATE-X and OlympiA trials [5••, 12•, 21••]. The combination of chemotherapy agents (such as capecitabine) and immune checkpoint inhibitors (ICI, like pembrolizumab) has been studied broadly and it is known to be safe; however, the efficacy of this combination in the post-neoadjuvant setting is unknown [16]. Given that patients with residual disease often have a very poor prognosis, the combination can be considered after a careful discussion with the patients about the paucity of efficacy data. The combination of PARP inhibitors and ICIs has also been evaluated, with the rationale for this combination based on the fact that PARP inhibitors can modify the tumor immune microenvironment and tumor characteristics to enhance the tumor response to immunotherapy. The combination has shown to be safe based on different studies, although the only randomized trial thus far in breast cancer (metastatic setting) did not show superiority of the PARP inhibitor olaparib with the anti-PD-L1 atezolizumab

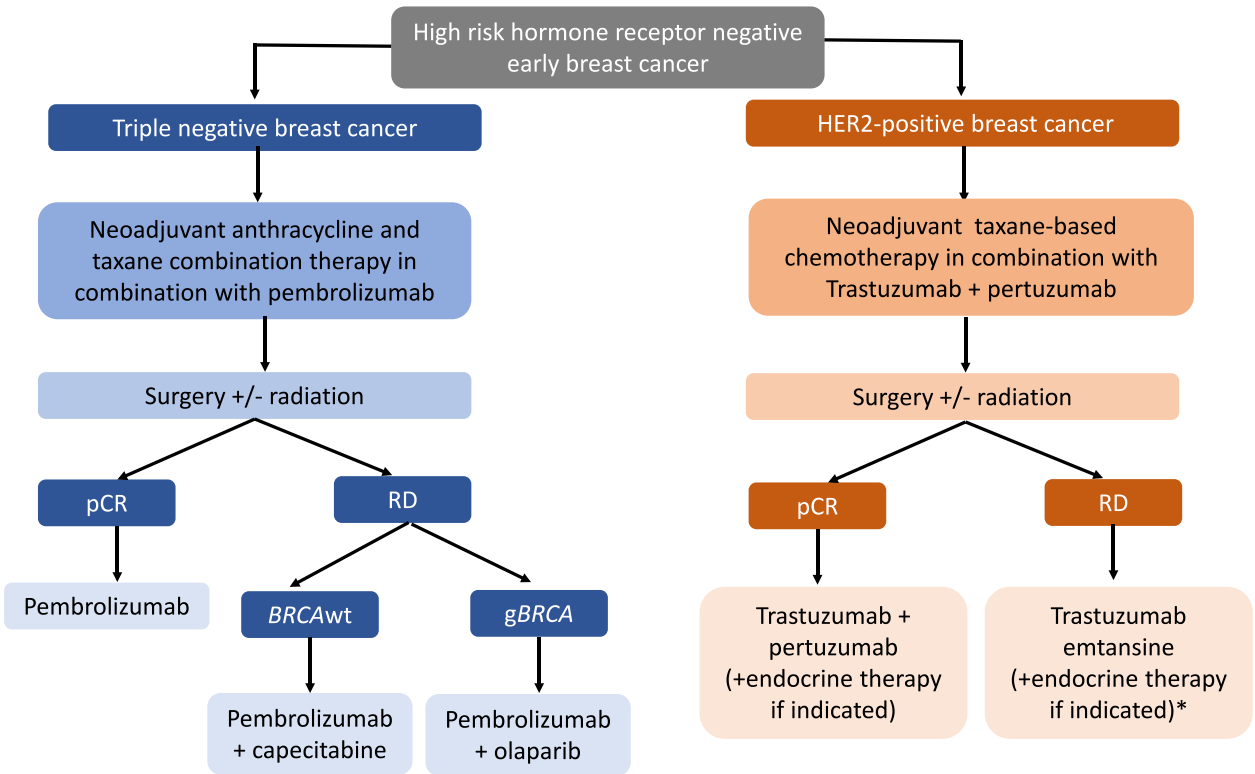

Fig. 1 Proposed treatment algorithm for early HER2-positive and triple-negative breast cancer. BRCAwt, *BRCA* wildtype; gBRCA, carrier of a pathogenic or likely pathogenic *BRCA* variant; HER2, human epidermal growth factor receptor 2; pCR, pathologic complete response; RD, residual disease. Asterisk (*) indicates that neratinib can be considered for selected patients with HER2 and hormone receptor positive HER2-positive breast cancer. Always consider participation in clinical trials

Table 1 Summary of selected studies for patients with residual disease after neoadjuvant therapy

Trial	Regimen	Patient population	Sample size (n)	Results
TNBC				
CREATE-X (UMIN000000843, phase 3) [5••]	Capecitabine 1250 mg/m^2 BID day 1–14 of 21 days for 6–8 cycles vs standard of care	Stage I–IIIb HR + or TNBC with any residual disease	887 overall (286 TNBC)	5-year DFS (TNBC): 69.8% (capecitabine) vs 56.1% (standard of care) (HR 0.58; 95% CI 0.39–0.87) 5-year OS (TNBC): 78.8% (capecitabine) vs 70.3% (standard of care) (HR 0.52; 95% CI 0.30–0.90)
ECOG-ACRIN EA1131 (NCT02445391, phase 3) [15••]	Non-inferiority study assessing carboplatin AUC 6 or cisplatin 75 mg/m^2 day 1 of 21 days for 4 cycles vs capecitabine 1000 mg/m^2 day 1–14 of 21 days for 6 cycles	Stage II or III with at least 1 cm of residual disease	391	3-year IDFS: 42% (platinum) and 49% (capecitabine)
OlympiA (NCT02032823, phase 3) [21••, 28]	Olaparib 300 mg BID vs placebo for 1 year	Stage I to III, HR + or HR − , with documented germline mutation in *BRCA1* or *BRCA2*	1836 (921 in olaparib group)	4-year IDFS: 82.7 (olaparib) vs. 75.4% (placebo) 3.5-year DRFS: 86.5 (olaparib) vs 79.1% (placebo) 4-year OS: 89.8 (olaparib) vs 86.4% (placebo)
BRE09-146 NCT01074970, phase 2 [29]	Cisplatin 75 mg/m^2 day 1 of 21 days for 4 cycles + rucaparib day 1, 2, and 3 of 21 days for 4 cycles vs cisplatin 75 mg/m^2 day 1 of 21 days for 4 cycles	Stage I to III	128 (57 in rucaparib + cisplatin group)	DFS: rucaparib 64.1% vs placebo 54.2% ($p = 0.29$)
HER2-Positive				
KATHERINE (NCT01772472, phase 3)	T-DM1 3.6 mg/kg on day 1 of 21 days vs trastuzumab 6 mg/kg day 1 of 21 days for 14 cycles	Stage I–Stage IIIc (excluding T1aN0 and T1bN0). HR + or HR-	1486 (743 in T-DM1 group)	IDFS: 88.3% with TDM1 vs 77% with trastuzumab (HR 0.50; 95% CI 0.39–0.64, $p < 0.001$) Distant recurrence as first invasive disease event in 10.5% of T-DM1 patients vs 15.9% trastuzumab patients OS has not yet surpassed the early reporting boundary, 5.7% vs 7.5% at 5 years

TNBC triple-negative breast cancer, *IDFS* invasive disease-free survival, *DFS* disease-free survival, *DRFS* distant recurrence-free survival, *OS* overall survival, *TTDR* time to distant recurrence, *CNS* central nervous system, *pCR* pathologic complete response, *EFS* event-free survival

compared to olaparib alone [23, 25, 30]. Based on these findings and the promising results of the KEYNOTE-522 and the OlympiA studies, the combination can be considered for patients with residual disease after neoadjuvant chemoimmunotherapy; however, again, limitations about the lack of efficacy data need to be discussed with patients. Finally, the combination of chemotherapy and PARP inhibitors has been attempted and has not been successful due to intolerable toxicities [31]; therefore, the combination of olaparib and capecitabine is not recommended outside of a clinical trial.

Several trials are ongoing to determine the optimal treatment for patients with residual disease after neoadjuvant therapy for TNBC, with most assessing combination therapies in this setting. Some examples are included in Table 2. Examples include trials combining post-neoadjuvant immunotherapy with antibody–drug conjugates (ADC) such as the ASCENT-05/OptimICE-RD/AFT-65 trial (NCT05633654) and A-Brave studies (NCT05633654, NCT2926196) that are assessing the role of the TROP2-ADC sacituzumab govitecan in combination with ICIs in this setting, or the TROPION-Breast03 trial (NCT05629585) that is evaluating the role of datopotamab deruxtecan, a different TROP2-ADC, with the anti-PD-L1 durvalumab. Another attractive approach is being studied in the PERSEVERE trial (NCT04849364) in which individual ctDNA results are being utilized to guide post-neoadjuvant treatment.

HER2-Positive Breast Cancer

Current Adjuvant Treatment Options for Patients with HER2-Positive and Residual Disease After Neoadjuvant Therapy

The standard treatment for patients with HER2-positive tumors larger than 2 cm and/or with lymph node involvement is neoadjuvant combination chemotherapy and dual HER2-directed monoclonal antibodies. Given the risk for cardiotoxicity and secondary malignancies, the use of anthracyclines has fallen out of favor for most patients and the more commonly used standard of care regimen consists of a carboplatin, taxane, trastuzumab, and pertuzumab containing regimen [32–34]. This regimen is associated with a pCR rate of approximately 55–65% [34]. There are ongoing studies (COMPASSHER-pCR [NCT04266249] and MARGOT [NCT04425018]) assessing the efficacy in pCR and long-term outcomes of regimens including a single chemotherapy agent (a taxane) and dual HER2-directed monoclonal antibodies. As standard of care, after neoadjuvant therapy, patients undergo surgery and radiation therapy. The post-neoadjuvant therapy is then tailored to the individual patient response to therapy. Endocrine therapy is added to the post-neoadjuvant therapy when appropriate.

The continuation of HER2-directed monoclonal antibodies has shown to improve long-term outcomes of patients with early HER2-positive breast cancer. The current standard is to continue HER2-targeted treatment for 1 year. In terms of treatment selection, the addition of pertuzumab to trastuzumab showed an improvement in long-term outcomes for patients with lymph node involvement at diagnosis, regardless of HR status in the APHINITY trial [35•]. Assessing lymph node status prior to initiation of chemotherapy has some limitations, and it has been reported that up to 25% of patients with small, clinically negative HER2-positive tumors are found to have lymph node involvement at the time of surgery [36]. Therefore, the decision to continue dual HER2-directed therapy needs to be individualized for each patient.

For patients with residual disease, the phase 3 KATHERINE trial assessed the role of trastuzumab vs the HER2-targeted ADC trastuzumab emtansine (T-DM1) for 14 cycles in 1486 patients with residual disease after neoadjuvant therapy (over 70% HR-positive and only 18% received pertuzumab) [6••]. In this study, the iDFS was 88.3% in the T-DM1 arm and 77% in the trastuzumab arm (HR 0.5, 95% CI 0.39–0.64, $p < 0.001$). Notably, around half of the patients treated with T-DM1 who experienced distant recurrence had central nervous system (CNS) disease, highlighting that this as an area of unmet need in HER2-positive disease. A recently presented updated analysis at a median follow-up of 8.4 years revealed a 7-year iDFS of 67.1 vs 80.8% (HR 0.54, 95% CI 0.44–0.66, $p < 0.0001$); OS was 84.4 vs 89.1% (HR 0.66, 95% CI 0.51–0.87, $p = 0.0027$) [37••]. Patients treated with T-DM1 had higher rates of thrombocytopenia and neuropathy as well as more adverse events leading to drug discontinuation. Based on the findings from KATHERINE, T-DM1 was approved by the U.S. FDA for the treatment of patients with HER2-positive breast cancer and residual disease in May of 2019 and a recent analysis confirms that this treatment is associated with improved long-term outcomes [37••, 38].

Finally, HER2-directed small molecule tyrosine kinase inhibitors (TKI) have also been studied in patients with early HER2-positive breast cancer [39]. Neratinib is a pan-HER TKI that was studied in the extended adjuvant setting for patients with HER2-positive breast cancer in the ExteNET trial [39]. This was a phase 3 trial in which 2840 patients with early HER2-positive breast cancer (treated with neoadjuvant or adjuvant treatment) were randomized to receive 1 year of neratinib therapy (240 mg daily). At a median follow up of 8 years, patients treated with neratinib had a modest improvement in iDFS and a smaller number of CNS events. Notably, the benefit was only seen in patients with HR-positive disease and the benefit was greater if the treatment was started within 1 year of completion of trastuzumab therapy. Of note, the patients treated in this study did not receive pertuzumab or T-DM1 as a part of their neo(adjuvant) therapies, and therefore, the efficacy of this treatment for patients treated with newer agents is

Table 2 Selected ongoing studies for patients with early-stage breast cancer who received neoadjuvant therapy and have residual disease

Trial	Regimen	Patient population	Status
TNBC			
ASCENT-05 / optimiICE-RD (NCT05633654, phase 3)	Sacituzumab-govitecan + pembrolizumab vs pembrolizumab + / − capecitabine	Stage I to III	Ongoing recruitment, results pending Estimated primary completion July 2027
TROPION-Breast03 (NCT05629585, phase 3)	Datopotumab-deruxtecan with or without durvalumab vs investigators choice of therapy	Stage I to III	Recruiting
A-Brave (NCT02926196, phase 3)	Avelumab vs observation	Stage I to III	Not actively recruiting, awaiting results
NCT04437160, phase 2	Epirubicin or pirarubicin + cyclophosphamide vs observation	Stage I to III neoadjuvant treatment with platinum + taxane ≥ 1 cm residual disease	Ongoing recruitment, results pending Estimated primary completion January 2026
PERSEVERE (NCT04849364, phase 2)	Arm 1a: DNA repair pathway = talazoparib + capecitabine. Arm 1b: immunotherapy pathway = atezolizumab + capecitabine. Arm 1c: PI3K pathway = inavolisib + capecitabine → atezolizumab. Arm 1d: DNA repair + Immunotherapy = talazoparib + atezolizumab + capecitabine. Arm 2: not genomically available treatment. Arm 3: No ctDNA detected	Stage I–III. At least 1 cm of residual disease or macroscopic lymph node involvement or RCB 2–3	Recruiting
BreastImmune03 (NCT03818685, phase 2)	Nivolumab + ipilimumab vs capecitabine	Stage I to III Not previously treated with immunotherapy	Not actively recruiting, awaiting results publication
OXEL (NCT03487666, phase 2)	Nivolumab vs capecitabine vs nivolumab + capecitabine	Stage I to III Not previously treated with capecitabine or immunotherapy	Not actively recruiting, awaiting results publication
EMPOWER (NCT04333706, phase 2)	Sarilumab + capecitabine vs capecitabine	Stage I to III	Concurrent phase 1 study evaluating sarilumab in metastatic disease Not actively recruiting, awaiting results publication
UNITY (NCT03945721, phase 1)	Niraparib daily with radiation	Stage I to III (excluding T1aN0, T1bN0)	Actively recruiting
NCT04674306, early phase 1	Alpha-lactalbumin vaccine	Stage II and III	Actively recruiting
HER2-Positive			
CompassHER2 RD (NCT04457596, phase 3) [9]	Tucatinib + T- DM1 vs placebo + T-DM1	Stage I to III If HR +, must be node positive	Ongoing recruitment, results pending Estimated Primary completion January 2028
DESTINY-Breast05 (NCT04622319, phase 3)	T-DM1 vs T-DXd	Patients with residual disease after 6 cycles of therapy	Recruiting
NCT04197687, phase 2	TPIV100 vaccine vs placebo + sargamostim + T-DM1	Stage II and III	Ongoing recruitment, results pending Estimated Primary completion January 2025

TNBC triple-negative breast cancer

unknown. This option can be considered for patients with high-risk, HR-positive, and HER2-positive disease. Another consideration is the toxicity profile of neratinib, particularly notable for significant diarrhea and dose escalation and/or a prophylactic regimen should be considered based on the CONTROL study [40]. Figure 1 shows our current treatment algorithm for patients with HER2-positive breast cancer and residual disease, and Table 1 summarizes the trials. Current clinical questions are discussed in the next section.

Future Directions and Ongoing Trials

Even though significant advances have been made in the treatment of patients with early HER2-positive breast cancer, there is still an opportunity for improvement, with a particular emphasis on the prevention of distant recurrences, particularly CNS disease. HER2-directed TKIs have shown to have CNS activity and combining an ADC with a TKI in the post-neoadjuvant setting is an attractive alternative [41]. The role of T-DM1 with or without the TKI tucatinib is being studied in the COMPASSHER2-RD trial (NCT04457596). A new generation of ADCs has been developed, and the HER2-directed ADC trastuzumab deruxtecan (T-DXd) has shown to be more effective than T-DM1 in treating patients with advanced HER2-positive disease [42]. These ADCs are being compared in the DESTINY-Breast05 trial (NCT04622319). Several other approaches are being investigated and summarized in Table 2.

In terms of biomarkers, circulating DNA (ctDNA) has shown promise in predicting long-term outcomes in early breast cancer. The phase 2 c-TRAK TN trial (NCT03145961) assessed the role of ctDNA surveillance in patients with stage II–III TNBC. Here, patients with positive ctDNA were randomized 2:1 to pembrolizumab or observation [43]. A total of 161 (out of 171 in the study) patients had ctDNA sequencing; the rate of mutations was 27.3% ($n=44$). From those 45 enrolled in the therapeutic component, none of the patients achieved ctDNA clearance with pembrolizumab. At the time of ctDNA detection, 72% of patients were found to have metastatic disease. This study suggested that ctDNA has a potential clinical utility in detecting early metastatic disease; however, major limitations of this study are the lack of serial staging scans and the small sample size. In the OXEL trial, ctDNA was used to determine if patients with residual disease after neoadjuvant chemotherapy had minimal residual disease (MRD) and this phase 2 study showed that the presence of MRD was associated with higher relapse rates [17•].

Circulating tumor cells (CTCs) are another biomarker with the potential of detecting early relapses in breast cancer. In a study of 30 healthy donors and 28 patients with early breast cancer (mostly HR positive) [44], CTC clusters were identified in 5 patients and single CTCs in 16 patients. Of interest, there was 94% concordance with the HR-status of the primary tumor and 100% with HER2. This study was a proof of concept; additional research is needed to determine if the detection of CTCs is associated with worse outcomes. At this time, it is unclear whether a systemic intervention based on early detection of ctDNA/CTC improves long-term outcomes of patients with early breast cancer. These tests are not routinely used in clinical practice, and several trials are ongoing to determine their clinical utility. A concern with using them at this point outside of a clinical trial is that although it has been established that they are associated with a worse prognosis, it is not clear whether an intervention could change the patient's prognosis. Therefore, results could increase anxiety for patients without a known intervention to improve outcomes.

Conclusion

The treatment of early breast cancer has evolved significantly, and patient outcomes continue to improve. As better treatments are developed, we will need biomarkers to determine which patients may benefit from certain therapies in order to continue to improve outcomes by right-sizing treatments and limiting toxicities.

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Declarations

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