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CLINICAL TRIALS (JE LANG, SECTION EDITOR)

Recent Developments in HER2-Directed Therapy in Breast Cancer

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Abstract

Purpose of Review This review will discuss recent important trials for the treatment of HER2-positive breast cancer, emphasize ongoing areas of development, and highlight areas of unmet need.

Recent Findings Advances for early-stage treatment have been driven by key clinical trials with pertuzumab, neratinib, and TDM-1. In the adjuvant setting, dual HER2 targeting with trastuzumab and pertuzumab has demonstrated modest improvement in disease-free survival. Neratinib also showed modest benefit in the extended adjuvant setting after prior trastuzumab. Finally, for patients who did not achieve pathologic complete response to neoadjuvant therapy, adjuvant therapy with TDM-1 showed significant disease-free survival benefit over trastuzumab. In advanced disease, neratinib appears to have activity beyond standard second line treatment. Promising compounds with early-phase data reviewed are tucatinib, margetuximab, and antibody-drug complexes. Immunotherapy in HER2-positive disease also has early-phase data. Endocrine therapy in combination with CDK4/6 inhibition and HER2-targeted therapy is in evaluation. Two areas of unmet need include CNS disease and disease treatment in the elderly population.

Summary In the wake of recent practice changing clinical trials, HER2-directed therapy is rapidly evolving. Future advances in therapy are anticipated with ongoing studies.

Keywords HER2-positive breast cancer · Adjuvant therapy · Targeted therapy · Metastatic disease · CNS metastasis

Introduction

Human epidermal growth factor receptor 2 (HER2) is a tyrosine kinase receptor overexpressed in a significant number of breast cancers and is associated with aggressive clinical phenotype. Prior to HER2-directed therapy, prognosis was poor for patients with HER2 overexpression [1]. The introduction of HER2-directed therapy was a landmark turning point in the treatment of HER2-positive breast cancer. Trastuzumab, a monoclonal antibody targeting the HER2 oncoprotein, was the first approved HER2-targeted treatment and rapidly became part of standard first-line treatment in the advanced disease setting based on a landmark study demonstrating longer time to disease progression of 7.4 months with trastuzumab vs 4.6 months without trastuzumab and a 5-month improvement in survival (25.1 vs 20.3 months) [2]. Subsequent trials earned approval in the neoadjuvant and adjuvant setting [3–7]. For example, in the Neoadjuvant Herceptin (NOAH) trial, rate of pathologic complete response (pCR) was doubled with the addition of trastuzumab to standard neoadjuvant chemotherapy (43% vs 23%, $p = 0.002$) [8]. In the adjuvant setting, the addition of trastuzumab to anthracycline-containing chemotherapy in the Breast Cancer International Research Group (BCIRG) 006 trial resulted in 5-year disease-free survival of 84% vs 75% (hazard ratio, 0.66; $p = 0.002$) [6]. HER2 amplification is found in 15–20% of all breast cancer patients [9]. With such an appealing target, several other HER-2 targeting therapies have been developed including pertuzumab, neratinib, and T-DM1. In this article, we review recent data on the use of HER2-targeted therapies in the adjuvant, neoadjuvant, and metastatic settings and changing paradigms in the treatment of HER2-positive disease.

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Adjuvant Setting

Multiple studies established 12 months of adjuvant trastuzumab as the standard of care in HER2-positive patients [4–6, 10–12]. Overall survival benefit of 12 months of adjuvant trastuzumab combined with adjuvant chemotherapy was demonstrated in a planned joint analysis of the NSABP B-31 and NCCTG N9831 trials. In HERA, 2 years of trastuzumab did not significantly improve disease-free survival compared with 1 year of trastuzumab after 8 years of follow-up [5]. Recent investigations have demonstrated improvement in patient outcomes through the utilization of newer HER2-directed therapies in place of and in addition to trastuzumab and have been adopted into national guidelines such as those of the National Comprehensive Cancer Network (NCCN) [13].

Lapatinib is tyrosine kinase inhibitor of HER2. In the NeoALTTO trial, lapatinib in combination with trastuzumab given neoadjuvantly was shown to increase rates of pCR over trastuzumab alone 51.3% vs 29.5% $p = 0.001$ [14]. In ALTTO, adjuvant lapatinib was given concurrently with trastuzumab for 1 year, or sequentially for 8.5 months after 3 months of trastuzumab and did not significantly improve disease-free survival compared with trastuzumab after a median follow-up of 4.5 years [12]. Based on the negative results of the ALTTO trial, lapatinib is not recommended for use in the neoadjuvant or adjuvant setting.

Pertuzumab is a monoclonal antibody that binds the domain of HER2 where it binds to HER3, preventing HER2/HER3 dimerization [15]. The APHINTY trial examined the addition of pertuzumab to adjuvant trastuzumab and chemotherapy, a combination informed by significant improvements in the pCR rates with pertuzumab in the neoadjuvant setting [16••,17,18]. This large, placebo-controlled international study enrolled 4805 patients with node-positive or high-risk node-negative (histologic or nuclear grade 3, hormone receptor negative, age < 35) disease. Patients were randomized to either pertuzumab or placebo added to standard adjuvant chemotherapy plus 1 year of treatment with trastuzumab. Therapy with pertuzumab was shown to improve upon the primary endpoint of 3-year invasive disease-free survival (DFS) with a rate of 94.1% compared with 93.2% in the placebo arm (hazard ratio [HR] 0.81, $p = 0.045$). Preplanned subgroup analysis did not show benefit for patients with node-negative or hormone receptor–positive status. Overall survival (OS) data has not yet matured. The addition of pertuzumab did come with increased risk of adverse events, particularly diarrhea, with grade 3 or higher events seen in 9.8% of patients treated with trastuzumab and pertuzumab and 3.7% of patients treated with trastuzumab alone. No significant, additional cardiac toxicity was noted [16••]. The FDA granted approval for adjuvant pertuzumab based on this trial.

Neratinib, an irreversible pan-HER tyrosine kinase inhibitor, was approved for extended adjuvant therapy based on the pivotal phase III trial ExteNET. The primary endpoint of 2-year invasive disease-free survival (iDFS) was reported in 2016 followed by an exploratory 5-year analysis in 2017 [19•, 20]. The study enrolled patients with early-stage HER2-positive breast cancer who had completed adjuvant trastuzumab-based therapy within 2 years and randomized them to 1 year of neratinib oral tablets 240 mg daily versus placebo. During its course, the study underwent amendments to restrict enrollment to node-positive disease and trastuzumab completion within 1 year, in order to capture a higher risk population and early recurrences, respectively. This was partly based on the BCIRG 006 trial results for early-stage HER2 positive which showed node-negative patients had excellent prognosis with modern therapy [21]. The primary endpoint of 2-year iDFS in the intent to treat population was 94.2% in the neratinib-treated group and 91.9% for the placebo-treated group for an absolute benefit of 2.3% and hazard ratio of 0.66, $p = 0.008$ [19•]. This benefit was maintained at the exploratory 5-year analysis where iDFS was 90.5% in the neratinib group and 87.7% for placebo for an absolute benefit of 2.5% [20]. Of note, the important endpoint of distant disease-free survival was only a 1.7% benefit in favor of neratinib at 5 years (91.6% with neratinib vs 89.9% for placebo). More compelling was the pre-specified subgroup analysis in which hormone receptor–positive disease appeared to benefit more than hormone receptor negative. Five-year iDFS was 90.8% with neratinib versus 85.7% with placebo resulting in an absolute benefit of 5.1% and hazard ratio (HR) of 0.58. No benefit was found in the hormone receptor–negative group. It is postulated that crosstalk between the HER2 signaling and estrogen receptor (ER)–mediated signaling may be responsible for the improved benefit of neratinib in hormone receptor–positive disease. As HER2 signaling is inhibited, ER signaling is upregulated and is a possible resistance mechanism. Therefore, dual blockade of HER2 and ER may be a more effective strategy in preventing breast cancer recurrence [22]. ExteNET reported high rates of diarrhea on neratinib with 40% of patients experiencing grade 3 or higher diarrhea. Dose reductions were required in 31% of patients with 28% having to discontinue neratinib altogether. The benefit of neratinib may have been mitigated by substantial difficulty managing drug side effects. Currently, primary diarrhea prophylaxis is recommended with neratinib and various prophylactic regimens are being evaluated in the CONTROL trial [23]. Results thus far suggest that much of the toxicity can be mitigated with appropriate supportive care. Guidelines are reserved regarding extended adjuvant neratinib and allow consideration in hormone receptor–positive HER2-positive disease perceived to be at high risk. However, the benefit for patients who received pertuzumab or T-DM1 is unknown [13].

Trastuzumab emtansine (T-DM1) is an antibody-drug conjugate of trastuzumab and the cytotoxic microtubule inhibitor emtansine. KATHERINE was a phase III randomized adjuvant therapy enrolling neoadjuvant therapy-treated patients with residual invasive disease after surgery [24••]. The trial enrolled 1486 patients who were randomized to receive T-DM1 or trastuzumab. The primary endpoint was 3-year invasive disease-free survival IDS; it was achieved in 88.3% of patients receiving T-DM1 versus 77% of patients receiving trastuzumab (HR 0.50, $p < 0.001$). Patients with inoperable breast cancer were included in the study and consisted of ~ 25% of the population. At the time of the interim analysis, no significant difference was noted for overall survival but further follow-up is required. Eighteen percent of patients discontinued T-DM1 due to varied side effects. The most common reasons for drug discontinuation were thrombocytopenia (4.2%) and liver function test abnormalities. T-DM1-treated patients had increased risk of sensory neuropathy of any grade (18.6%) versus those receiving trastuzumab (6.9%). The large benefit found in this study led to FDA approval for T-DM1 in the adjuvant setting for patients with residual disease after neoadjuvant trastuzumab-based chemotherapy.

Duration of Adjuvant Therapy

While the standard duration of adjuvant trastuzumab is 12 months, more recent studies have examined the potential for shorter duration of HER2 therapy in the interest of reducing toxicities, especially cardiac. Limiting the duration of therapy seeks to balance efficacy, cost, and toxicity of therapy [25,26,27•]. Two large European studies, PHARE and PERSEPHONE, compared efficacy of 6 versus 12 months of adjuvant trastuzumab in patients with HER2-positive, resectable invasive breast cancers. Both were designed as non-inferiority studies with the primary endpoint of disease-free survival (DFS) with patients enrolled in a 1:1 intervention to control ratio [25, 27•].

In the PHARE study, enrolling 3384 patients in 156 French centers, 6 months of adjuvant trastuzumab was not shown to be inferior to 12 months of therapy [25]. The non-inferiority margin was set at 2% for 2-year DFS with a hazard margin of 1.15. Study accrual was halted early due to concern for negative efficacy in the 6-month treatment group. At 2 years, DFS events were 8.9% for 6 months of treatment and 6.2% for 12 months (HR1.28, $p = 0.29$). This analysis did not meet the prespecified hazard margin and the study was unable to demonstrate non-inferiority. In a final analysis, with a median follow-up of 7.5 years, non-inferiority was again not reached [28•]. DFS-related events were noted in 21.2% of the 6-month treatment group and 20.4% of the 12-month treatment group (adjusted HR 1.08, $p = 0.39$) which included the non-inferiority margin, thus leading to conclusion of a negative study. Further subgroup analysis did not identify any significant variation. Cardiotoxicity events were fewer in the 6-month group versus 12 months.

By contrast, the PERSEPHONE study, which enrolled 4089 patients in 152 United Kingdom centers, demonstrated non-inferiority of 6 versus 12 months of adjuvant trastuzumab therapy [27•]. After a median follow-up of 5.4 years, DFS-related events were noted in 12% of the 6-month treatment group and 13% of the 12-month treatment group. The study was designed and powered to detect a non-inferiority margin of 3% for 4-year DFS HR1.29. The primary analysis showed 4-year DFS to be 89.4% with 6 months adjuvant therapy and 89.8% with 12 months. The HR was 1.07 ($p = 0.011$), which did not exceed the preset limit of 1.29, so the authors declared that 6 months of treatment was non-inferior to 12 months. Notably, subgroup analysis suggested potential benefit to 12 months of adjuvant trastuzumab for patients who received adjuvant taxane-only based therapy or concurrent rather than sequential trastuzumab. A lower proportion of grade 3 toxicity events was noted in the 6 month group (19%) versus 12 month group (24%) with fewer patients also requiring discontinuation of trastuzumab therapy due to cardiotoxicity (6 months—3%, 12 months—8%).

PHARE and PERSEPHONE represent the most extensive analysis of HER2 de-escalation to date; however, more study will be required in order to change the current standard of care. Both studies enrolled similar patients with respect to age, nodal status, and tumor size (~ 90% < 5 cm). Notably, the chemotherapy regimens employed were quite different from current practice. In PHARE, 73% of patients received anthracycline/taxane-based adjuvant therapy compared with only 43% of patients in PERSEPHONE. Adjuvant therapy has evolved significantly based on the APHINITY, ExteNET, and KATHERINE trials described earlier. Pending further evaluation, the standard duration of HER2 therapy remains 1 year. However, findings do suggest that for low-risk patients or those intolerant of HER2 therapy, shorter duration may confer relatively minimal disadvantage.

Neoadjuvant Setting

The combination of chemotherapy and HER2 therapy has significantly improved the rate of pCR when used in the neoadjuvant setting [3, 8, 14, 29–33]. Patients who achieve pCR have significantly improved EFS and OS [34, 35]. The Neosphere and TRYPHAENA studies demonstrated improved rates of pCR with the addition of pertuzumab to chemotherapy and trastuzumab in the neoadjuvant setting and have become the standard of care [17, 18]. In the Neosphere trial, the addition of pertuzumab to docetaxel and trastuzumab resulted in 39.3% pCR vs 21.5% without pertuzumab; $p = 0.0063$. In TRYPHAENA, pCR rates with trastuzumab and pertuzumab in combination with various multiagent

chemotherapy regimens were 54.7–63.6%. Inclusion criteria in these trials were tumors ≥ 2 cm and/or node positive. The roles of newer HER2-targeted agents and other treatment modalities are yet to be established.

Lapatinib has been studied extensively in the neoadjuvant setting with multiple phase II and III studies demonstrating improved rates of pCR [14, 29–31]. In a meta-analysis by Hickes et al., the pooled rate of pCR for lapatinib added to trastuzumab plus neoadjuvant chemotherapy was 55.8% vs 38.4% with trastuzumab plus neoadjuvant chemotherapy [36]. However, FDA approval has not been given to this combination possibly due to increased toxicity and lack of benefit in disease-free or overall survival in the adjuvant setting (see ALTTO trial above).

The biosimilars are now incorporated into the NCCN guidelines as appropriate substitutes for trastuzumab for any trastuzumab-containing systemic therapy options [13]. The first product approval was based on a study in the neoadjuvant setting demonstrating the biosimilar SB3 compared with trastuzumab resulted in breast pCR rate within the prespecified equivalence margin. The rates of breast pCR were 51.7% with SB3 and 42.0% with trastuzumab resulting in the confidence interval of adjusted ratio of breast pCR within the predefined equivalence margins. Safety and toxicity by serious adverse events and treatment-emergent adverse events were similar for both groups [37•]. At time of this publication, five compounds are FDA-approved for use as trastuzumab biosimilars and are featured in Table 1 [38].

An experimental regimen of dual HER2-targeted therapy with T-DM1 and lapatinib was examined in the TEAL study. In this study, 30 patients were randomized to 6 weeks of T-DM1 plus lapatinib followed by 12 weeks of weekly paclitaxel with T-DM1 and lapatinib vs 6 weeks of trastuzumab plus pertuzumab followed by 12 weeks of weekly paclitaxel with trastuzumab and pertuzumab. Primary objective of residual cancer burden (RCB) 0 or 1 was 100% in the experimental arm vs 62.5% with standard therapy ($p = 0.0035$). The study was halted early on recommendation of the data safety monitoring committee due to the observed superior efficacy in the experimental arm. Interestingly in the ER positive cohort, all patients on the experimental arm achieved RCB 0 or 1 compared with only 25% in the standard therapy arm [39]. Based on these impressive preliminary results, further study of this regimen is warranted.

Table 1 FDA-approved trastuzumab biosimilars

Brand name	Biosimilar	Approval date (FDA)
Herzuma (trastuzumab-pkrb)	CT-P6	December 2018
Kanjinti (trastuzumab-anns)	ABP 980	June 2019
Ogivri (trastuzumab-dkst)	Myl14010	December 2017
Ontruzant (trastuzumab-dttb)	SB3	January 2019
Trazimera (trastuzumab-qyyp)	PF-05280014	March 2019

Neratinib was studied in the neoadjuvant setting in the I-SPY2 trial, a multicenter adaptive phase II trial with pCR rate as its primary endpoint. Among HER2-positive, hormone receptor–negative patients, neratinib resulted in a pCR rate of 56% when added to standard neoadjuvant chemotherapy, compared with 33% with standard chemotherapy and trastuzumab. This met the pre-specified efficacy threshold resulting in "graduation" for phase 3 testing [40]

The KRISTINE trial was a randomized, open-label, phase 3 study that internationally enrolled 444 patients with stage II–III operable HER2-positive cancer (tumor size > 2 cm) [41•]. This study compared the combination of T-DM1 and pertuzumab, a novel combination of targeted-therapy omitting standard chemotherapy, versus standard of care treatment with combination chemotherapy (docetaxel and carboplatin) with trastuzumab and pertuzumab (TCHP). The primary endpoint was the rate of pCR. Secondary endpoints were proportion of patients without inflammatory breast cancer who had breast-conserving surgery, patient-reported outcomes related to quality of life, and safety assessments. The rate of pCR was 44% with T-DM1 and pertuzumab versus 55.7% for TCHP for an absolute difference of − 11.3% ($p = 0.016$). Breast-conserving surgery was performed in fewer patients on the T-DM1 and pertuzumab regimen (42%) than patients receiving TCHP (53%). Unsurprisingly, the omission of traditional chemotherapy resulted in lower rates of adverse events, with grade 3 or higher noted in 13% in the T-DM1 and pertuzumab arm and 64% with TCHP. Key clinical outcomes such as DFS and OS are pending further follow-up. Nonetheless, this study suggests that, even at the cost of greater toxicity, chemotherapy remains a key component of neoadjuvant therapy for invasive breast cancer.

Further investigation is being directed towards decreasing toxicity, treatment, and costs associated with therapy [42]. Taking pCR as an indicator of improved prognosis, patients who achieve this result may be appropriate for less chemotherapy. The currently accruing pilot study, DAPHNe (NCT03716180), aimed at personalizing therapy for patients who may not need standard chemotherapy. Patients with stage II to III HER2-positive breast cancer are given neoadjuvant paclitaxel with trastuzumab and pertuzumab for 12 weeks followed by surgery for assessment of pathologic response. Those who achieve pCR will then complete 1 year of dual antibody therapy (HP) in the adjuvant setting. Patients not achieving pCR undergo additional adjuvant chemotherapy and HP for 1 year. The primary outcome is adherence to protocol-specified therapy in the pCR group. Select secondary outcomes include pCR and RCB rate, event-free survival (EFS), recurrence-free interval (RFI), and OS.

Several other studies are examining risk-adapted therapy de-escalation with various systemic regimens such as weekly

carboplatin and paclitaxel with trastuzumab and pertuzumab in BrUOG 308(NCT02789657), and TRAIN-3 (NCT03820063). Omission of radiation is being examined in the setting of pCR (Selective Use of Observation After Lumpectomy and Sentinel Lymph Node Biopsy in Her-2 Positive Patients With Pathologic Complete Response to Neoadjuvant Chemotherapy NCT03460067). Even the elimination of surgery is being examined in the setting of good response to neoadjuvant treatment (Multicenter Trial for Eliminating Breast Cancer Surgery in Exceptional Responders With Neoadjuvant Systemic Therapy, NCT02945579).

Table 2 highlights currently enrolling studies in HER2-positive, early-stage disease.

Metastatic Setting

As detailed previously, HER2-directed therapy was rapidly adopted based on initial advances in the metastatic setting. Further advances have since been made with the use of novel agents and combinations.

Pertuzumab

In the first-line setting, the CLEOPATRA trial established the utility of the addition of pertuzumab to trastuzumab and docetaxel compared with trastuzumab and docetaxel plus placebo. There was an unprecedented survival benefit of 15.7 months with OS of 56.5 months in the pertuzumab group compared with 40.8 months in the placebo group (HR = 0.68; $p < 0.001$) [43]. Improvement in PFS of 18.5 months with pertuzumab compared with 12.4 months in the control group accompanied this marked survival benefit and have established this regimen as standard of care in the first-line setting.[44]

Lapatinib

Lapatinib is approved for use in the metastatic setting most commonly in combination with capecitabine after initial therapy. This was based on a phase III study in which patients with metastatic HER2-positive breast cancer that had progressed on prior anthracycline, taxane, and trasuzumab were randomized to lapatinib plus capecitabine vs capecitabine alone. The primary endpoint was time to progression which was 27.1 months with lapatinib vs 18.6 months with capecitabine alone ($p = 0.00013$) [45].

TDM-1

In EMILIA and TH3RESA, TDM-1 demonstrated its efficacy in populations pretreated with trastuzumab [46, 47]. EMILIA compared TDM-1 with lapatinib and capecitabine (LC) in patients previously treated with trastuzumab and taxane therapy. PFS was improved in the TDM-1 group (T-DM1 9.6 months, LC 6.4 months) with further OS benefit (T-DM1 30.9 months, LC 25.1 months) and improved toxicity profile (grade 3 toxicity: TDM-1 41%, LC 57%) [47]. TH3RESA tested TDM-1 versus investigator's choice in patients who had received at least 2 prior HER2-directed therapies including trastuzumab and lapatinib with substantial OS benefit (TDM-1 22.7 months, choice 15.8 months) [46]. The results of these 3 trials are even more impressive given substantial cross-over to the intervention arms versus comparison.

Neratinib

Recent early reports of the NALA trial demonstrated the efficacy of neratinib versus lapatinib when either was used in combination with capecitabine for metastatic HER2-positive disease progressed on ≥ 2 prior lines [48•]. Neratinib and capecitabine demonstrated improved PFS compared with lapatinib and capecitabine with evidence of increasing benefit over time (6 months—47.2% versus 37.8%, 12 months 28.8% versus 14.8%). OS at 12 months was 28.8% for neratinib- and capecitabine-treated patients versus 14.8% for lapatinib and capecitabine treated patients. Lessons in using diarrheal prophylaxis were taken from previous experiences with neratinib in ExteNET. Patients received mandatory diarrheal prophylaxis with grade 3 diarrhea reported in 24.4% and only 2.5% discontinuing treatment due to diarrhea. By comparison, in ExteNET, grade 3 diarrhea was reported in 40% and 28% discontinued treatment due to diarrhea [19•]. Additionally, the TBCRC 022 trial reported data on CNS activity of the combination of neratinib and capecitabine [49]. In this phase 2 study, patients with measurable, progressive HER2-positive brain metastases (majority had received prior neurosurgery and/or radiation) were treated with neratinib 240 mg po daily plus capecitabine 750 mg/m2 twice per day for 14 days, then 7 days off. There were two cohorts: lapatinib-naïve and lapatinib-treated, and the primary endpoint was composite central nervous system (CNS) ORR. Forty-nine patients enrolled in the lapatinib-naïve cohort, demonstrating composite CNS ORR of 49%, while the lapatinib-treated cohort demonstrated composite CNS ORR of 33% ($n = 12$). Taken together, these studies suggest that neratinib plus capecitabine is an important combination in metastatic HER2-positive breast cancer.

Tucatinib

Tucatinib is a potent tyrosine kinase inhibitor of HER2. Due to its strong HER2-selectivity over EGFR, tucatinib is associated with much less rash and diarrhea. In a phase 1b study of tucatinib with capecitabine and trastuzumab in patients

Table 2 Select phase 2/3 neoadjuvant/adjuvant clinical trials in HER2-positive breast cancer

Trial information	Setting	Information	Primary endpoint(s)	Study start date
BrUOG 308: Efficacy of Weekly Carboplatin and Paclitaxel With Trastuzumab and Pertuzumab (wPCbTP) and Switching to an Anthracycline-based Regimen (AC) in Non-responding Patients as Neoadjuvant Therapy in Clinical Stage I-III HER2-positive Breast Cancer. (NCT02789657)	Neoadjuvant	1) 18 weeks (6 cycles) of paclitaxel, carboplatin, trastuzumab, and pertuzumab. Post treatment, patients will undergo surgery. 2) 12 weeks (4 cycles) of paclitaxel, carboplatin, trastuzumab, and pertuzumab. Post 12 weeks, initiation of doxorubicin and cyclophosphamide for 4 cycles (6 weeks), followed by surgery.	pCR	December 2013
A Randomized Phase III Trial Evaluating Pathologic Complete Response Rates in Patients With Hormone Receptor-Positive, HER2-Positive, Large Operable and Locally Advanced Breast Cancer Treated With Neoadjuvant Therapy of Docetaxel, Carboplatin, Trastuzumab, and Pertuzumab (TCHP) With or Without Estrogen Deprivation (NCT02003209)	Neoadjuvant	1) Docetaxel, carboplatin, trastuzumab, and pertuzumab × 6 cycles → surgery, radiation, and trastuzumab to 1 year 2) Docetaxel, carboplatin, trastuzumab, and pertuzumab x6cycles → surgery, radiation, trastuzumab to 1 year, gosrelin acetate, and aromatase inhibition	pCR	January 15, 2014
Chemotherapy-free Trastuzumab and Pertuzumab in HER2-positive (Human Epidermal Receptor) Breast Cancer: FDG-PET Response-adapted Strategy. The PHERGain Study (NCT03161353)	Neoadjuvant	1) Pertuzumab, trastuzumab, carboplatin, and docetaxel × 4 cycles PET: pertuzumab, trastuzumab, and endocrine × 12 cycles 2) pertuzumab, trastuzumab, and endocrine × 2 cycles PET responders: pertuzumab, trastuzumab, and endocrine × 6 cycles. CR: pertuzumab, trastuzumab, and endocrine × 10 cycles Non-CR: pertuzumab, trastuzumab, carboplatin, and docetaxel × 6 cycles. Pertuzumab, trastuzumab, and endocrine × 4 cycles. PET non-responders: pertuzumab, trastuzumab, carboplatin, and docetaxel × 6 cycles. Pertuzumab, trastuzumab, and endocrine × 10 cycles	pCR, 3-year iDFS	June 26, 2017
A Phase III, Randomized, Double-Blind, Placebo-Controlled Clinical Trial To Evaluate the Efficacy and Safety Of Atezolizumab or Placebo in Combination With Neoadjuvant Doxorubicin + Cyclophosphamide Followed By Paclitaxel + Trastuzumab + Pertuzumab In Early Her2-Positive Breast Cancer (NCT03726879)	Neoadjuvant and adjuvant	1) Neoadjuvant: atezolizumab and ddAC × 4 cycles → atezolizumab and paclitaxel-HP × 4 cycles. Adjuvant: atezolizumab and HP to 1 year (or atezolizumab and T-DM1 to 1 year) 2) Neoadjuvant: placebo and ddAC × 4 cycles → placebo and paclitaxel-HP × 4 cycles. Adjuvant: placebo and HP to 1 year (or placebo and T-DM1 to 1 year)	pCR in PD-L1-positive population, pCR in ITT	January 11, 2019
Neoadjuvant Her2-targeted Therapy and Immunotherapy With Pembrolizumab (neoHIP) (NCT03747120)	Neoadjuvant	1) Paclitaxel weekly × 12 + Trastuzumab + Pertuzumab 2) Paclitaxel weekly × 12 + trastuzumab + pertuzumab + pembrolizumab	pCR	January 25, 2019
Image-guided De-escalation of Neo-adjuvant Chemotherapy in HER2-positive Breast Cancer: the TRAIN-3 Study (NCT03820063)	Neoadjuvant	Paclitaxel, carboplatin, trastuzumab, pertuzumab	3-year event-free survival	February 27, 2019
A Randomized Phase II Study of Trastuzumab Emtansine (T-DM1) vs. Paclitaxel in Combination With Trastuzumab for Stage I HER2-Positive Breast Cancer – ATEMPT (NCT01853748)	Adjuvant	1) T-DM1 × 51 weeks (17 cycles) 2) Paclitaxel, trastuzumab × 12 weeks (12 cycles), and trastuzumab to 1 year	DFS	May 15, 2013
A Randomized, Multicenter, Open-Label, Phase III Trial Comparing Trastuzumab Plus Pertuzumab Plus a Taxane Following Anthracyclines Versus Trastuzumab	Adjuvant	1) FEC, EC or AC × 3–4 cycles, taxane × 3–4 cycles with HP to 1 year 2) FEC, EC, or AC × 3–4 cycles, T-DM1 and pertuzumab to 1 year	iDFS overall, iDFS node-positive	January 31, 2014

Table 2 (continued)

Trial information	Setting	Information	Primary endpoint(s)	Study start date
Emtansine Plus Pertuzumab Following Anthracyclines as Adjuvant Therapy in Patients With Operable HER2-Positive Primary Breast Cancer (NCT01966471)				
A Multicenter Phase II Study of Vaccines to Prevent Recurrence in Patients With HER-2 Positive Breast Cancer (NCT03384914)	Adjuvant	1) DC1 vaccine 2) WOKVAC vaccine	DFS	February 9, 2018
ATOP TRIAL: Adjuvant Ado-Trastuzumab Emtansine (T-DM1) for Older Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer (NCT03587740)	Adjuvant	≥ 60 years old, T-DM1 q3 weeks	5-year iDFS	August 22, 2018

Search conducted on clinicaltrials.gov—HER2-positive breast cancer, recruiting/active—not recruiting, interventional studies, adult, phase 2/3

previously treated with T-DM1, trastuzumab activity was seen including in 7 of 9 patients with brain metastases [50, 51]. ORR was 58% in 24 patients with measurable disease including 1 CR. Common toxicities were diarrhea, palmar plantar erythrodysesthesia, and fatigue. Based on these data, the HER2Climb (NCT02614794) study is evaluating tucatinib versus placebo in combination with capecitabine and trastuzumab and is open to patients regardless of CNS involvement.

Immunotherapy

The host anti-tumor response plays a role in the effectiveness of HER2-directed therapy. HER2-positive disease has a higher mutational burden and tumor infiltrating lymphocyte (TIL) level than hormone positive disease. As in Fig. 1, trastuzumab and pertuzumab exert an antibody-dependent cellular cytotoxicity (ADCC) effect of which may then further stimulate the immune response through causation of cell death with antigen and cytokine release. Accordingly, some data have shown correlation with TIL levels and benefit of trastuzumab therapy [52–55].

The emerging wave of immunotherapy has not neglected HER2-positive breast cancer; the PANACEA trial is a phase 1b/2 trial that evaluated trastuzumab combined with pembrolizumab in patients with previous disease progression on trastuzumab [56•]. The initial enrollment consisted of a 3 + 3 dose escalation for pembrolizumab. Subsequently, a protocol amendment led to dosing of pembrolizumab at the commonly used dose of 200 mg IV every 3 weeks combined with trastuzumab therapy. A total of 52 patients were enrolled; 40 were PD-L1 positive and 12 PD-L1 negative. Overall response in PD-L1-positive patients was 15% with no responses seen in the PD-L1-negative group. While demonstrating salvageable HER2 therapy response in some patients, further studies are needed to establish the role of immunotherapy in HER2-positive breast cancer. Studies of checkpoint inhibitors are ongoing such as NRG-BR004 (NCT03199885) examining front-line atezolizumab with taxane plus trastuzumab and pertuzumab for metastatic disease. Immunotherapy is also being studied in the neoadjuvant setting with agents like atezolizumab (NCT03726879) and pembrolizumab (NCT03747120). Combination approaches of checkpoint inhibitors with agents such as costimulatory antibodies (utomilumab, PRS-343) or tumor vaccines are also under investigation in clinical trials.

Vaccines are also an attractive immune therapeutic strategy with the potential to activate both the innate and adaptive immune system [57]. In preclinical models, Berzofsky et al. demonstrated an adenoviral vector vaccine expressing the extracellular and transmembrane domains of HER2 was curative in mice with large established HER2-positive tumors. In a phase I trial of the vaccine for HER2-expressing solid tumors naïve to trastuzumab, clinical benefit was seen in 54% of patients at the 2nd and 3rd dose escalations [58]. Part 2 of the study in patients (mostly breast cancer) with prior trastuzumab is under way. Across trials, thus far, safety seems acceptable with adverse reactions limited to mostly injection site reactions, fatigue, and fevers/chills/rigors. No cardiac signal has been appreciated suggesting that vaccines are a tolerable treatment strategy [59].

Margetuximab

Margetuximab is an investigational antibody targeting HER2 with an engineered Fc region designed to increase affinity for the activating Fc receptor CD16A while decreasing affinity for an inhibitory receptor CD32B. A majority of HER2-positive

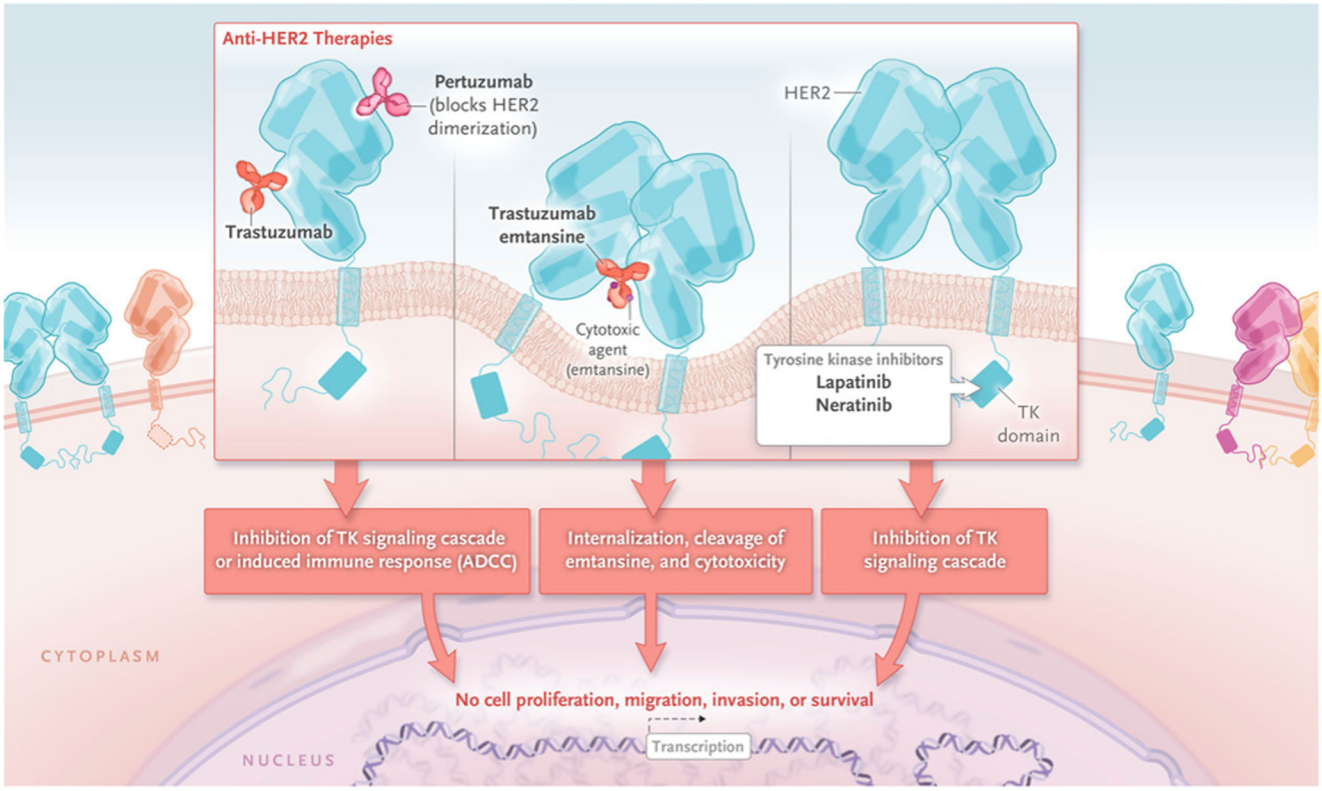

Fig. 1 Anti-HER2 therapies and mechanism of action. The binding locations and mechanisms of action of anti-HER2 agents are shown. The antibody-based trastuzumab, pertuzumab, and trastuzumab emtansine bind to the extracellular domain. The tyrosine kinase inhibitors lapatinib and neratinib cross the cellular membrane. Trastuzumab and pertuzumab inhibit the tyrosine kinase signaling cascade and/or induce antibody-dependent complement-mediated cytotoxicicty. Trastuzumab emtansine is internalized and emtansine cleaved leading to cytotoxicity. After crossing the cell membrane, lapatinib and neratinib inhibit tyrosine kinase signaling cascade. From The New England Journal of Medicine, DF Hayes, HER2 and Breast Cancer: A Phenomenal Success Story, 381, 1284-1286, Copyright (2019) J Medical Society. Reprinted with permission from Massachusetts Medical Society

patients carry the CD16A 158F allele, which has a lower binding affinity and has been associated with decreased response to trastuzumab. Margetuximab improves engagement of the innate immune system and enhances ADCC. SOPHIA (NCT02492711) is a phase 3 open-label study that enrolled 536 patients with HER2-positive metastatic breast cancer who had received prior pertuzumab [60]. Patients were randomized 1:1 to margetuximab or trastuzumab in combination with one of four chemotherapy agents (capecitabine, eribulin, gemcitabine, or vinorelbine) given at the standard dose. Primary endpoints are centrally assessed PFS and OS. Secondary endpoints are PFS by investigator assessment and ORR. For the primary endpoint of PFS, margetuximab and chemotherapy resulted in 5.8 months compared with 4.9 months for trastuzumab and chemotherapy (HR = 0.76, p = 0.033). In a pre-specified exploratory analysis of the subpopulation with CD16A 158F allele, PFS was 6.9 months versus 5.1 months (HR = 0.68, p = 0.005). The secondary endpoint of ORR was 22% in the margetuximab arm versus 16% with trastuzumab. OS data was not mature at time of this publication. Safety between the two arms was comparable with grade 3 or greater AEs in 52% of patients on the margetuximab arm compared with 48% in the trastuzumab arm. Infusion-related reactions were more common with margetuximab (13%) than trastuzumab (4%) but were mostly grade 1 or 2. In summary, margetuximab plus chemotherapy was found to improve PFS compared with trastuzumab plus chemotherapy in patients with metastatic HER2-positive breast cancer with progression after prior trastuzumab and pertuzumab. Benefit appears to be enhanced in low-affinity CD16A-158F carriers.

Antibody-Drug Conjugates

Several antibody-drug conjugates are in clinical trials with promising responses in heavily pretreated and even HER2-low expressing tumors.

Trastuzumab deruxtecan (DS-8201) is a novel antibody-drug conjugate with a humanized HER2 antibody attached to a topoisomerase I inhibitor payload by a peptide-based linker. In 2015, a phase 1 study (NCT02564900) was initiated to evaluate the safety and efficacy of DS-8201a in subjects with advanced HER2-expressing or HER2-mutated solid tumors (gastric, gastro-esophageal, and breast). In 2019, Tamura and colleagues reported on the safety and efficacy of 115

patients with HER2-postive breast cancer with disease resistant to trastuzumab emtansine who received ≥ 1 dose of DS-8201a. ORR was 59.5% in 111 patients evaluable for response (95% CI 49.7–68.7), median PFS was 22.1 months (range 0.8–27.9), and median time to response was 1.6 months (95% CI 1.4–2.8). Toxicities noted in this cohort included 20 cases of interstitial lung disease, pneumonitis, or organizing pneumonia, including two treatment-related deaths. Grade 3 or 4 cytopenias were also noted: anemia 17%, neutropenia 14%, and thrombocytopenia 8%. Treatment discontinuation related to adverse events occurred in 13 patients (11%) showing overall reasonable tolerability of this regimen. The enrolled patients had all received prior trastuzumab emtansine and 86% had received prior pertuzumab with a median of 7 prior anticancer regimens [61]. In this heavily pretreated cohort, such response rates are certainly promising.

This trial also included HER2-low (HER2 IHC 1+ or 2+/ISH-negative) breast cancer. Thirty-four patients with HER2-low breast cancer were treated on protocol with median 2 prior endocrine therapies and 3 prior chemotherapies. The majority (85%) of this population had HR-positive disease of which 17% had received prior CDK4/6 inhibitor. The ORR in this group was 50.0% with a disease control rate of 85.3%, median duration of response was 11 months and median PFS was 12.9 months [62].

DS-8201a is currently being evaluated in two phase 3 trials. DESTINY-Breast02 compares DS-8201a with physician's choice (trastuzumab plus capecitabine or lapatinib plus capecitabine) in patients with HER2-positive, unresectable, and/or metastatic breast cancer previously treated with standard of care HER2 therapies including T-DM1. DESTINY-Breast03 compares DS-8201a with T-DM1 in disease previously treated with trastuzumab and taxane.

SYD985, another antibody-drug conjugate, has demonstrated impressive results in the phase I setting. ORR was 33% in HER2-positive cohort, 40% in HER2-low, hormone receptor–negative and 28% in HER2-low, hormone receptor–positive [63]. TULIP (NCT03262935), a phase 3 study, compares SYD985 with physician's choice therapy in HER2-positive unresectable locally advanced or metastatic breast cancer. The primary objective is to demonstrate superior PFS. Secondary objectives are OS, ORR, patient-reported outcomes, and safety and tolerability.

Several other antibody-drug conjugates such as A166, ALT-P7, ARX788, DHES0815A, DS-8201a, RC48, MEDI4276, and XMT-1522 targeting HER2 are in development as well [64]. Many have excellent preclinical data and promising clinical data but have varying toxicity profiles. As studies of these HER2-targeting antibody-drug conjugates mature, their role in clinical treatment will be clarified. Of particular interest is their activity in HER2-low tumors. To date, no HER2-targeted therapies have been approved for HER2-low tumors. The NSABP B-47 phase 3 study compared adjuvant chemotherapy with or without a year of trastuzumab in women with node-positive or high-risk node-negative invasive breast cancer that was HER2-low. This study failed to show a benefit for trastuzumab in HER2-low disease [65].

Endocrine Therapy

For the subset of patients who are hormone receptor–positive and HER2-positive, endocrine therapy (ET) in combination with HER2 therapy is under evaluation. In PERTAIN, a phase 2 trial, patients with hormone receptor–positive, HER2-positive metastatic or locally advanced breast cancer were treated with first-line aromatase inhibitor (AI) and randomized to trastuzumab or the combination of trastuzumab with pertuzumab. Prior induction chemotherapy was allowed. The primary endpoint was PFS and stratified median PFS was 15.8 months in the trastuzumab arm and 18.9 months in the trastuzumab with pertuzumab arm (HR = 0.65, p = 0.007) [66]. This demonstrated efficacy of AI in combination with HER2-targeted therapy and future report of secondary outcomes are anticipated. Impressive improvements in PFS seen with cyclin-dependant kinase (CDK) 4/6 inhibition in combination to ET provide an attractive alternative to chemotherapy in patients with both hormone receptor and HER2 positivity [67–69]. The PATINA (AFT-38/NCT02947685) trial is evaluating the addition of palbociclib to anti-HER2 and ET maintenance after induction therapy in the first-line setting. Patients will be given 6-8 cycles of chemotherapy and HER2 therapy followed by ET and HER2-directed therapy plus or minus palbociclib (a CDK4/6 inhibitor approved for metastatic hormone receptor–positive HER2 negative metastatic breast cancer). Primary outcome is PFS and accrual began in 2017.

Unmet Needs

Active studies for metastatic disease are highlighted in Table 3. Two specific areas of unmet need within metastatic HER2-positive disease are central nervous system (CNS) metastasis and the elderly population. Clinical trials in these arenas are needed to better address these populations.

CNS metastasis occurs in a higher proportion of HER2-positive breast cancers than other subtypes with over one-third of patients developing this feared complication [70, 71]. The etiology is unclear but brain metastasis appears to be related to longer survival and duration of HER2 therapy as these metastases tend to occur later in the time course. Hypothesized mechanisms include poor penetration of the blood-brain barrier by conventional HER2 therapies such as trastuzumab and loss of HER2 expression in brain metastases [71, 72]. Current recruiting studies include the addition of GDC-0084, a PI3-kinase inhibitor, to trastuzumab for brain metastases (NCT03765983), tucatinib plus lapatinib

Table 3 Select phase 2/3 clinical trials in metastatic or locally advanced HER2-positive breast cancer

Trial information	Therapy type/treatment setting	Background	Primary endpoint(s)	Study start date
A Randomized Phase II Trial of Pertuzumab in Combination With Trastuzumab With or Without Chemotherapy, Both Followed by T-DM1 in Case of Progression, in Patients With HER2-positive Metastatic Breast Cancer (NCT01835236)	ADCC	1) Trastuzumab and pertuzumab then 2nd line T-DM1 2) Trastuzumab, pertuzumab, and paclitaxel or vinorelbine then 2nd line T-DM1	OS	March 3, 2013
A Multi-centre, Open-label, Randomized Clinical Trial Comparing the Efficacy and Safety of the Antibody-drug Conjugate SYD985 to Physician's Choice in Patients With HER2-positive Unresectable Locally Advanced or Metastatic Breast Cancer - TULIP (NCT03262935)	ADCC, novel	1) SYD985 (vic-)trastuzumab duocarmazine 2) Physician's choice	PFS	November 30, 2017
A phase III study comparing trastuzumab emtansine with trastuzumab, pertuzumab, and docetaxel in elderly patients with advanced stage HER2-positive breast cancer- HERB TEA (JCOG1607)	ADCC	Elderly 65–79 years old 1) T-DM1 2) THP	OS	January 12, 2018
DS-8201a Versus T-DM1 for Human Epidermal Growth Factor Receptor 2 (HER2)-Positive, Unresectable and/or Metastatic Breast Cancer Previously Treated With Trastuzumab and Taxane - DESTINY-Breast03 (NCT03529110)	ADCC, novel	1) DS-8201a 2) T-DM1	PFS	July 20, 2018
DS-8201a in Pre-treated HER2 Breast Cancer That Cannot be Surgically Removed or Has Spread - DESTINY-Breast02 (NCT03523585)	ADCC, novel	1) DS-8201a—trastuzumab deruxtecan 2) Trastuzumab and capecitabine 3) Lapatinib and capecitabine	PFS	August 1, 2018
A Randomized Phase II Study to Evaluate Efficacy of T-DM1 With or Without Palbociclib in the Treatment of Patients With Metastatic HER2 Positive Breast Cancer (NCT03530696)	ADCC, CDK4/6 inhibitor	1) T-DM1 and palbociclib 2) T-DM1	PFS	December 6, 2018
A Phase II Trial of Palbociclib in Combination With Trastuzumab and Endocrine Therapy in Patients With Previously-treated Locally Advanced or Metastatic HER2-positive Breast Cancer -- PATRICIA II (NCT02448420)	CDK4/6 inhibitor	1) Palbociclib, trastuzumab, and endocrine 2) Physician's choice	PFS	July 2015
A Phase 2, Randomized, Multicenter, 3-Arm, Open-Label Study to Compare the Efficacy of Abemaciclib Plus Trastuzumab With or Without Fulvestrant to Standard-of-Care Chemotherapy of Physician's Choice Plus Trastuzumab in Women With HR+, HER2+ Locally Advanced or Metastatic Breast Cancer – monarchER (NCT02675231)	CDK4/6 inhibitor	1) Abemaciclib, trastuzumab, and fulvestrant or abemaciclib and trastuzumab 2) Trastuzumab and standard of care chemotherapy	PFS	May 23, 2016
A Randomized, Open Label, Phase III Trial to Evaluate the Efficacy and Safety of Palbociclib + Anti-HER2 Therapy + Endocrine Therapy vs. Anti-HER2 Therapy + Endocrine Therapy After Induction Treatment for Hormone Receptor Positive (HR+)/HER2-Positive Metastatic Breast Cancer (NCT02947685)	CDK4/6 inhibitor	1) Palbociclib, + antiHER2 therapy (trastuzumab/pertuzumab) q3wks + endocrine therapy (letrozole, anastrozole, exemestane OR fulvestrant) 2) Placebo, + antiHER2 therapy (trastuzumab/pertuzumab) q3wks + endocrine therapy (letrozole, anastrozole, exemestane OR fulvestrant)	PFS	June 21, 2017
A Randomized, Multicenter, Double-Blind, Placebo-Controlled Phase II Study of the Efficacy and Safety of Trastuzumab Emtansine	Immunotherapy	1) T-DM1 and atezolizumab 2) T-DM1 and placebo	PFS, % adverse events	September 26, 2016

Table 3 (continued)

Trial information	Therapy type/treatment setting	Background	Primary endpoint(s)	Study start date
in Combination With Atezolizumab or Atezolizumab-Placebo in Patients With HER2-Positive Locally Advanced or Metastatic Breast Cancer Who Have Received Prior Trastuzumab and Taxane Based Therapy (NCT02924883)				
A Randomized, Phase II Study Comparing Trastuzumab and Vinorelbine in Combination With Avelumab or Avelumab and Utomilumab (41BB/CD137 Agonist), in Patients With HER2-positive Metastatic Breast Cancer Who Have Progressed on Prior Trastuzumab and Pertuzumab - AVIATOR (NCT03414658)	Immunotherapy, novel	1) Trastuzumab and vinorelbine 2) Trastuzumab, vinorelbine, and avelumab 3) Trastuzumab, vinorelbine, avelumab, and utomilumab 4) Trastuzumab, avelumab, and utomilumab	PFS	June 21, 2018
A Randomized, Double-Blind, Phase III Trial of Paclitaxel/Trastuzumab/Pertuzumab With Atezolizumab or Placebo in First-Line HER2-Positive Metastatic Breast Cancer (NCT03199885)	Immunotherapy	Pertuzumab, trastuzumab, paclitaxel, atezolizumab versus pertuzumab, trastuzumab, paclitaxel, placebo	PFS	March 12, 2019
A Phase III Randomized Study of TH (Paclitaxel and Trastuzumab) Versus THL (Paclitaxel, Trastuzumab and Lapatinib) in First Line Treatment of HER2-positive Metastatic Breast Cancer (NCT01526369)	TKI	1) Paclitaxel and trastuzumab 2) Paclitaxel, trastuzumab, and lapatinib	PFS	January 2012
A Phase II Trial of HKI-272 (Neratinib), Neratinib and Capecitabine, and Ado-Trastuzumab Emtansine for Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer and Brain Metastases (NCT01494662)	TKI, ADCC/CNS disease	1) Neratinib (high-dose) 2) Neratinib (low-dose) 3) Neratinib/Capecitabine 4) Neratinib/TDM-1	ORR	February 2012
Phase II Randomized Study of Whole Brain Radiotherapy/Stereotactic Radiosurgery in Combination With Concurrent Lapatinib in Patients With Brain Metastasis From HER2-Positive Breast Cancer - A Collaborative Study of NRG Oncology and KROG (NCT01622868)	TKI/CNS disease	1) WBRT or SRS2) Lapatinib ditosylate and WBRT or SRS	CR	July 26, 2012
Phase 2 Randomized, Double-Blinded, Controlled Study of Tucatinib vs Placebo in Combination With Capecitabine and Trastuzumab in Patients With Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Carcinoma – HER2CLIMB (NCT02614794)	TKI	1) Tucatinib, capecitabine, and trastuzumab 2) Placebo, capecitabine, and trastuzumab	PFS	January 28, 2016

Search conducted on clinicaltrials.gov—HER2-positive breast cancer, recruiting/active—not recruiting, interventional studies, adult, phase 2/3

(NCT01921335), radiotherapy plus lapatinib (NCT01622868), and T-DM1 plus metronomic temozolomide (NCT03190967).

Clinical trials inclusive of or specifically for the elderly population are lacking in oncology. Current studies in HER2-positive disease look at regimens that may balance toxicity with efficacy in treatment of the elderly. One such trial is the Japanese JCOG1607 HERB TEA study, which asks the question of whether T-DM1 might be a non-inferior and better tolerated first-line treatment than standard docetaxel, trastuzumab, pertuzumab regimen for patients 65 years of age or older [73]. The primary endpoint is OS with a non-inferiority margin of 1.3 in terms of HR. A similar phase 2 study, the ATOP trial, is accruing in the USA for older patients with early-stage HER2-positive disease.

Conclusions

Treatment for HER2-positive breast cancer has made significant advances in both early and advanced stage disease with novel strategies targeting the HER2 pathway. The NCCN guidelines now include pertuzumab in the adjuvant setting for node-positive disease, consideration of neratinib for extended adjuvant therapy in high-risk hormone receptor–positive HER2-positive disease, and TDM-1 as adjuvant therapy instead of trastuzumab for patients with residual disease after trastuzumab-based neoadjuvant therapy [13]. Risk-adapted treatment, such as the use of T-DM1 for patients who fail to achieve pCR, may lead the way to future individualized, adaptive strategies. In the metastatic setting, novel agents such as neratinib, tucatinib, margetuximab, and antibody-drug conjugates have accumulating data. Immunotherapy combinations are being studied in both early-stage and advanced-stage disease. Endocrine therapy in combination with CDK4/6 inhibition is also being studied in combination with HER2-targeted agents. Finally, CNS disease and treatment of elderly populations remain areas of unmet need.

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Compliance with Ethical Standards

Conflict of Interest Irene Kang reports personal fees from Puma Biotechnology, and personal fees from Pfizer Inc. outside the submitted work. Janice Lu reports advisory roles for Novartis, Pfizer, Puma, Radius, and Daiichi outside the submitted work. Bing Xia reports personal fees from Genentech, personal fees from AstraZeneca, and other from Bristol-Myers Squibb outside the submitted work. Stephen Dong declares no conflicts of interest relevant to this manuscript.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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