

SYSTEMATIC REVIEW

ANTI-HER2 ANTIBODIES IN COMBINATION WITH CHEMOTHERAPY OR CHEMOTHERAPY-FREE REGIMENS TARGETING HER2-POSITIVE BREAST CANCER: A SYSTEMATIC REVIEW

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ABSTRACT

Breast cancer is the leading cause of cancer-related death in female worldwide. Human epidermal growth factor receptor 2 (HER2) amplification is observed in approximately 20% of breast cancer cases and is associated with poor clinical outcomes. Dual HER2 blockade without chemotherapy represents an attractive therapeutic approach, and it remains unresolved if anti-HER2 therapeutic antibodies are sufficient to replace chemotherapy regimens. In this review, we discuss the approved therapeutic monoclonal antibodies (pertuzumab and trastuzumab) and antibody-drug conjugate (trastuzumab emtansine or T-DM1) for the treatment of HER2-positive breast cancer patients. In summary, phase II and III clinical trials have demonstrated that dual HER2 blockade (pertuzumab and trastuzumab) plus chemotherapy regimens confer better efficacy compared with dual HER2 blockade alone, or anti-HER2 antibody monotherapy, in HER2-positive breast cancer patients. Dual HER2 blockade (pertuzumab and trastuzumab) combined with chemotherapies (5-fluorouracil, epirubicin, cyclophosphamide and docetaxel) yield superior response. Moreover, dual HER2 blockade (T-DM1 and pertuzumab) in combination with docetaxel represents a promising treatment regimen containing T-DM1. Ongoing clinical trials are assessing the optimal chemotherapy of choice with anti-HER2 antibodies combinations. In conclusion, improved outcomes are attributable to selection for the optimal chemotherapy regimen in combination with anti-HER2 antibodies instead of replacing chemotherapy altogether with the current line of anti-HER2 therapeutic antibodies.

Keywords: Breast cancer; HER2-positive; trastuzumab; pertuzumab; T-DM1

INTRODUCTION

Breast cancer is the most prevalent cancer and the leading cause of cancer-related death in female worldwide^{1,2}, and it accounts for approximately 30% of all new cancer cases³. Immunohistochemistry (IHC) detection of receptors is used to diagnose breast cancer including estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2)^{4,5}. *In situ hybridization* for *HER2* gene amplification is conducted either upfront or in IHC borderline cases⁶.

HER2 plays vital roles in cell growth and survival, and it is expressed at low levels in epithelial cells of certain normal human tissues^{7,8}. Amplification of *HER2* is observed in about 20% of breast cancer cases associated with worse outcomes^{9,10}, hence anti-HER2 therapeutic antibodies represent a rational therapeutic strategy for HER2-overexpressing breast cancer. The structure, functions and therapeutic antibodies targeting HER2 is presented in Figure 1.

The Food and Drug Administration (FDA)-approved therapeutic monoclonal antibodies (mAbs; trastuzumab and pertuzumab) and antibody-drug conjugate (ADC; trastuzumab emtansine or T-DM1) have enhanced the clinical response and outcomes of HER2-positive breast cancer patients. Dual HER2 blockade without chemotherapy represents an attractive therapeutic approach, and questions remain if anti-HER2 therapeutic antibodies are sufficient to replace chemotherapy regimens.

In this review, we present and discuss the mAbs (trastuzumab and pertuzumab) and ADC (T-DM1) targeting HER2-positive breast cancer to address the aforementioned issue. The series of phase II and III clinical trials either as single agents (monotherapy) or in combination with chemotherapy or chemotherapy-free regimens were shortlisted, described and discussed.

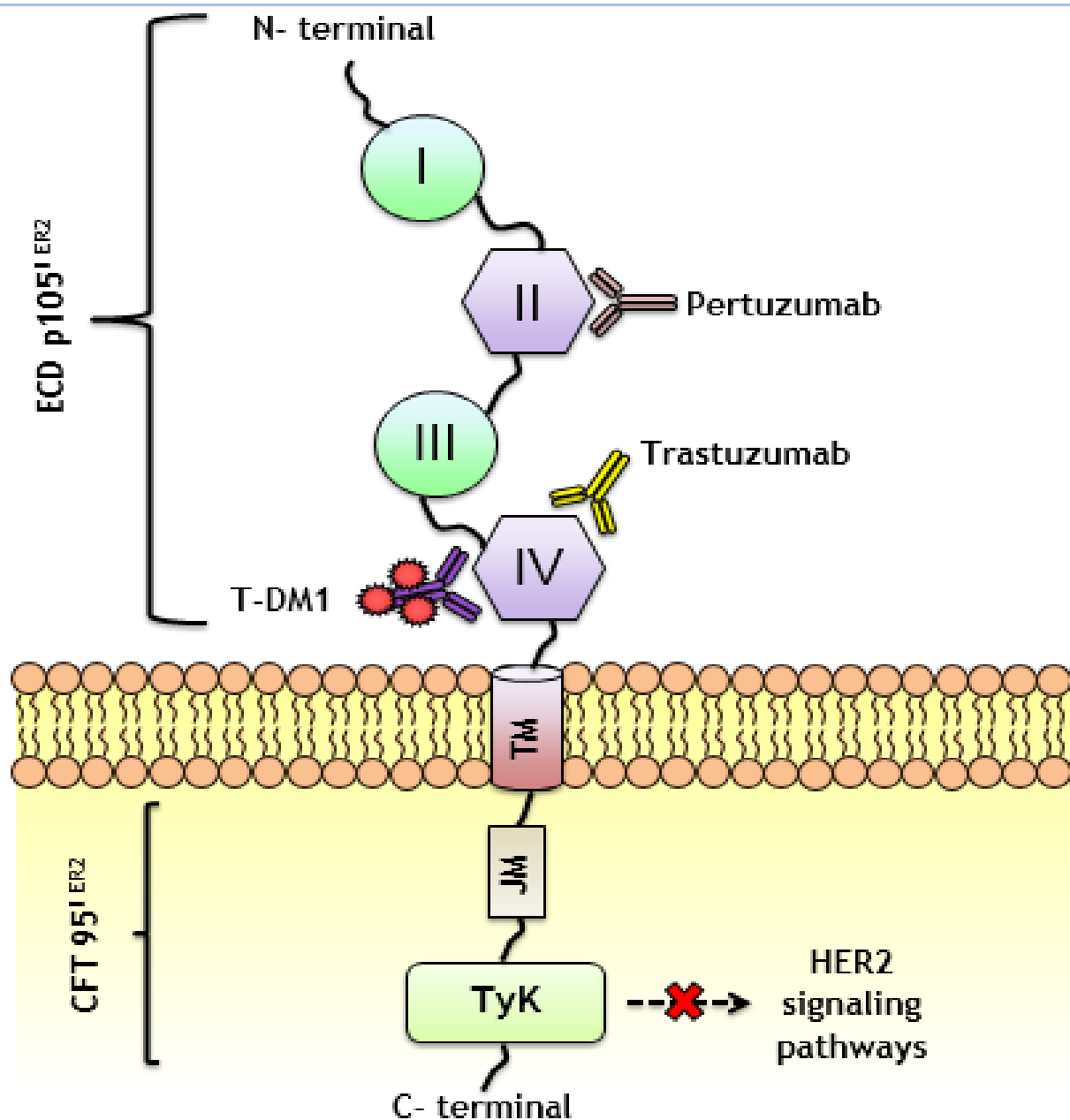


Figure 1: The structure and domains of HER2, and therapeutic antibodies targeting HER2.

HER2 is a type 1 transmembrane glycoprotein composed of three distinct regions *i.e.* N-terminal extracellular domain (ECD), a single α -helix transmembrane domain (TM), and an intracellular tyrosine kinase (TyK) domain. N-terminal ECD is divided into four subdomains (I-IV). Domains I and III are leucine-rich domains responsible for ligand binding while domains II and IV are cysteine-rich domains responsible for receptor dimerization. TM domain of HER2 is critically involved in HER2 signaling by stabilizing dimerization and also by

controlling structural reorganizations. Intracellular domain is composed of a cytoplasmic juxtamembrane (JM) linker, a tyrosine kinase (TyK) domain and a carboxyl-terminal tail (CFT). TyK domain autophosphorylation leads to the activation of tyrosine kinase downstream signaling pathways such as PI3K and MAPK pathways. Trastuzumab and T-DM1 target domain IV while pertuzumab targets domain II of HER2 to block its activation and downstream signaling pathways.

METHODS

For clinical trial studies, the electronic databases Google Scholar, PubMed, and ClinicalTrials.gov (<http://www.clinicaltrials.gov>) were used to search relevant literature using the following search terms: (breast cancer OR HER2 breast cancer OR metastatic breast cancer) AND (trastuzumab OR pertuzumab OR trastuzumab emtansine OR T-DM1) AND (monotherapy OR combination OR combination regimen). All articles were selected and reviewed in accordance with Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. All studies were searched and screened by two investigators (S.M.N.H., K.K.W.) independently, and disagreements were resolved through discussions by both investigators for a consensus. Only English language studies and clinical trials were included, and the literature was searched from inception to 22nd April 2019. Abstracts and proceedings were included while case reports, reviews, letters, editorials, observational, retrospective, pre-clinical or *in vitro* studies, other non-clinical trial studies, and studies without endpoint analysis were excluded. To identify additional relevant studies, the bibliographic references of all retrieved articles were manually searched, and the 'Cited by' function available on Google Scholar was utilized. A total of 55 studies met the inclusion criteria and they were included in this review (Figure 2).

Data was collected from the final shortlisted studies to gather the following information: types of anti-HER2 antibodies (*i.e.* trastuzumab, pertuzumab or T-DM1), phase, patient population (*i.e.* HER-2 positive early, metastatic breast cancer [MBC] or advanced disease), combination with chemotherapy or chemotherapy-free regimens, pre-treatment (*i.e.* with or without), endpoints (*i.e.* objective response rate [ORR], complete response [CR], partial response [PR], stable disease [SD], clinical benefit rate [CBR], progression-free survival [PFS], disease-free survival [DFS], overall survival [OS], pathological complete response [pCR]). The data was extracted by S.M.N.H. and K.K.W. independently, and each investigator cross-checked the data to confirm accuracy. All data was presented and compared as extracted without additional downstream statistical analysis.

RESULTS AND DISCUSSION

Trastuzumab

Trastuzumab (Herceptin) is the first FDA-approved recombinant mAb for the treatment of HER2-positive MBC. Trastuzumab is composed of two antigen-specific sites that bind to the juxtamembrane portion of the HER2 receptor extracellular domain (ECD) which blocks the activation of its intracellular tyrosine kinase domain^{11,12}. Trastuzumab binds to the domain IV of HER2 receptor which disrupts HER2

homodimerization and prevents the cleavage of ECD, thereby preventing the formation of p95^{HER2}, the active truncated receptor^{13,14}.

Trastuzumab monotherapy

A phase I trial of trastuzumab treatment in HER2-overexpressing MBC patients revealed that the tolerable dose of trastuzumab was 10-500mg in single dose or once weekly¹⁵. A subsequent phase II trial assessed the efficacy of single agent trastuzumab in HER2-positive breast cancer patients (n=43)¹⁶. The ORR was 11% including one achieving CR (2.3%). In a large, multinational phase II trial of trastuzumab treatment performed in women with HER2-positive MBC (n=222), 15% (n=33) achieved ORR, 3.6% (n=8) achieved CR and 11.7% (n=26) showed PR¹⁷.

Another phase II trial of trastuzumab monotherapy in HER2-overexpressing MBC patients (n=114) demonstrated ORR of 26%, with 6.1% achieved CR (n=7) and 20.2% achieved PR (n=23)¹⁸. Moreover, in a phase II trial assessing the efficacy of trastuzumab monotherapy (first-line treatment) in HER2-positive MBC (n=105)¹⁹. The ORR reported in the intent-to-treat population was 19% (1.9% CR, n=2; 17.1% PR, n=18), CBR was 33% and median time to progression was 3.4 months. The trastuzumab monotherapy given on a 3-weekly schedule was well tolerated.

The phase III randomized trial HERA (BIG 1-01) was an international, multicentre, open-label trial that enrolled patients with HER2-positive early breast cancer (n=5,102) after adjuvant chemotherapy, and 5,099 patients of the intent-to-treat population underwent follow-up for 11 years²⁰. The patients were randomly assigned (1:1:1) to receive trastuzumab for one year (n=1,702) or for two years (n=1,700), or to be in the observation group (without trastuzumab; n=1,697). One year of trastuzumab reduced the risk of a DFS event (HR=0.76; 95% CI: 0.68-0.86) and death (HR=0.74; 95% CI: 0.64-0.86), and improved DFS compared with the observation group (ten-year DFS 69% vs 63%, respectively). Two years of adjuvant trastuzumab did not improve DFS outcomes (HR=1.02; 95% CI: 0.89-1.17; ten-year DFS: 69%) compared with one year of trastuzumab²⁰. Hence, the long-term, 11-year follow-up demonstrated the lack of clinical benefits to prolong trastuzumab monotherapy treatment over a year that would expose patients to side effects.

Trastuzumab in combination with chemotherapy

A phase II trial assessed the safety profile of trastuzumab plus paclitaxel (administered for 12 weeks) followed by nine months of trastuzumab monotherapy in HER2-positive breast cancer patients (n=406). The primary endpoint of this study was 3-year invasive DFS (iDFS) reported to be 98.7% (n=401; 95% CI: 97.6-99.8%)²¹.

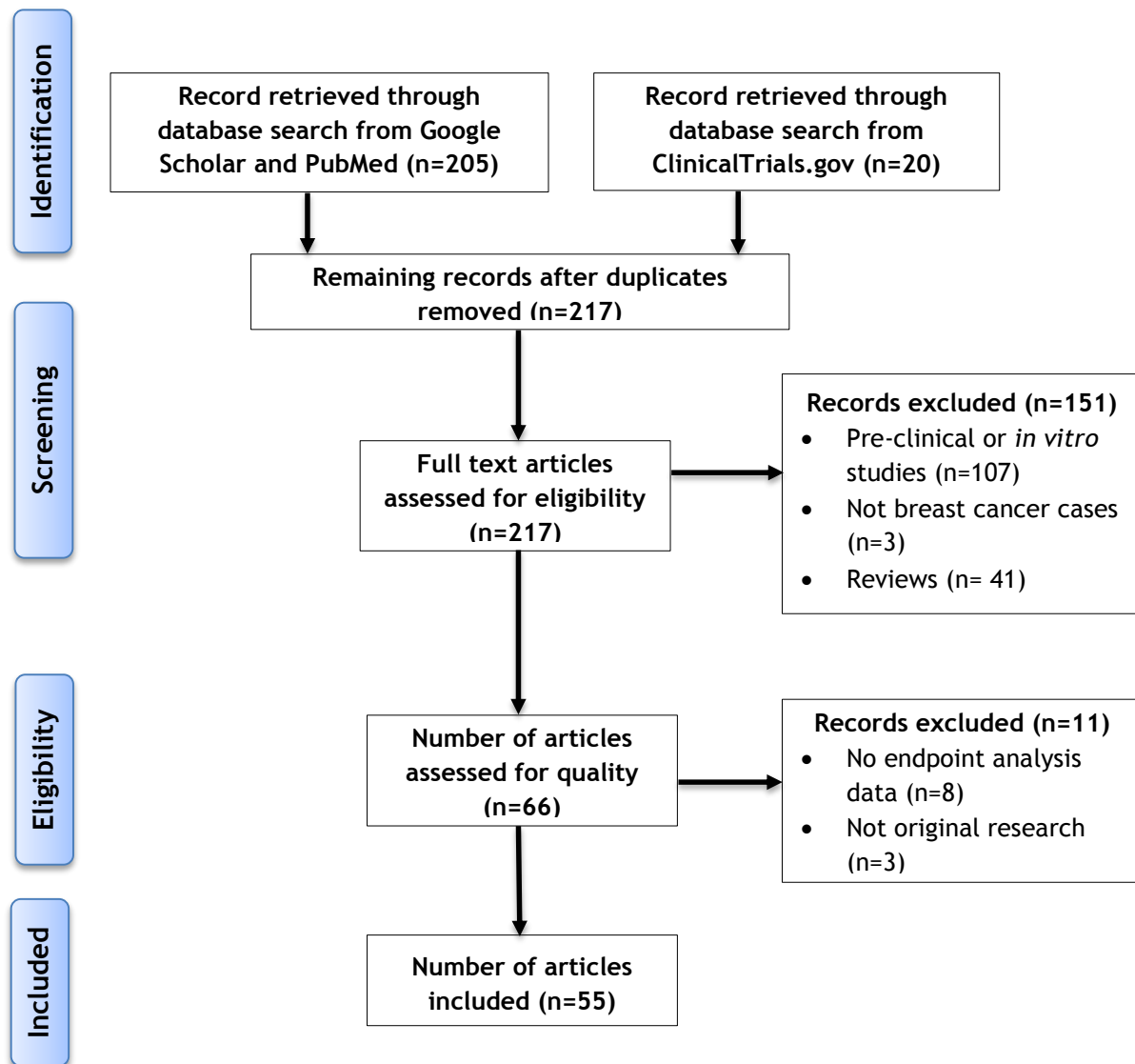


Figure 2: PRISMA flow diagram summarizing the study selection process.
A total of 55 articles were included in the review.

The phase II trial (NEfERT-T) was conducted in the first-line treatment of recurrent and/or HER2-positive MBC patients previously exposed to trastuzumab or lapatinib. This trial aimed to compare the efficacy of neratinib plus paclitaxel (n=242) and trastuzumab plus paclitaxel (n=237)²². The median PFS for both groups was 12.9 months (HR=1.02; 95% CI, 0.81-1.27; p=0.89), indicating that their clinical benefits in terms of PFS was comparable.

In a randomized phase III trial, the efficacy of trastuzumab and paclitaxel with or without carboplatin as first-line therapy was studied in HER2-overexpressing MBC patients (n=196). The ORR for trastuzumab-paclitaxel-carboplatin (TPC) was 52% (n=102) versus 36% (n=71) for trastuzumab-paclitaxel (TP). Meanwhile, the PFS was 10.7 months and 7.1 months for TPC and TP, respectively²³.

CALGB 40601 three-arm randomized phase III trial compared the combination of paclitaxel plus

trastuzumab (TH, n=120) with or without the addition of lapatinib (THL, n=118) to the control arm of paclitaxel plus lapatinib (TL, n=67) in stage II to III HER2-positive breast cancer patients 16 weeks before surgery²⁴. The pCR rate of THL, TH and TL was 56%, 46% and 32%, respectively. pCR of dual HER2-targeted therapy was not significantly higher than single HER2 targeting.

Another phase III trial (LUX-Breast 1) compared afatinib plus vinorelbine (n=339) with trastuzumab plus vinorelbine (n=169) in patients with HER2-overexpressing MBC who had progressed on prior adjuvant trastuzumab²⁵. The trastuzumab group exhibited enhanced median OS of 28.6 months compared with 19.6 months in afatinib group, however their median PFS and ORR were comparable (median PFS of 5.6 months vs 5.5 months; ORR of 47% vs 46%).

Trastuzumab in combination with chemotherapy free regimens

In recent years, growing number of clinical trials have combined trastuzumab with specific inhibitors. In a phase 1b trial, HER2-positive progressive breast cancer with prior trastuzumab, pertuzumab, and trastuzumab emtansine (n=60) were treated with tucatinib (HER2 tyrosine kinase inhibitor) in combination with capecitabine or trastuzumab²⁶. In patients with measurable disease, the achieved ORR for tucatinib-capecitabine combination was 83% (n=5 of 6 patients), but lower in tucatinib-trastuzumab combination with 40% (n=6 of 15 patients). However, the combinations had acceptable toxicity with preliminary anti-tumor activity. In a phase II study of trastuzumab-resistant HER2-positive advanced breast cancer, the patients (n=50) received both buparlisib (pan-class I PI3K inhibitor) and trastuzumab²⁷. The safety profile was acceptable but the primary endpoint of ORR $\geq 25\%$ was not achieved as the resulting ORR was only 10%, suggesting the requirement of chemotherapy to achieve better clinical outcomes.

Another phase III trial (NeoALLTO) was conducted on HER2-positive primary breast cancer patients receiving single agent lapatinib (n=154), trastuzumab monotherapy (n=149) or trastuzumab-lapatinib combination (n=152)²⁸. The pCR rate was higher in the combination group since 51.3% of the (n=78) patients achieved pCR compared with 29.5% in the group given trastuzumab alone (n=44). No significant difference was observed in pCR between the lapatinib and trastuzumab groups.

In a recent (2018) phase III trial, dual HER2 blockade was conducted with lapatinib plus trastuzumab (TRAS) combined with an aromatase inhibitor (AI) in postmenopausal women with HER2-positive/HR-positive MBC with prior endocrine treatment and prior neo(adjuvant)/first-line TRAS plus chemotherapy²⁹. Patients were randomly assigned to receive lapatinib+TRAS+AI (n = 120), TRAS+AI (n=117), or lapatinib+AI (n=118). Superior PFS was observed in lapatinib+TRAS+AI vs TRAS+AI (median PFS 11 vs 5.7 months; $p=0.0064$), and lapatinib+AI also showed better PFS compared with TRAS+AI (median PFS 8.3 versus 5.7 months; $p=0.0361$). Enhanced ORR, CBR, and OS were also observed in lapatinib+TRAS+AI group. The authors concluded that dual HER2 blockade was effective with tolerable safety profile.

As the immune checkpoint anti-PD-1 antibody pembrolizumab has shown remarkable efficacy in a number of solid tumors, combination of pembrolizumab with trastuzumab for the treatment of trastuzumab-resistant HER2-positive MBC patients (n=58) has recently been assessed in a phase Ib/II study as described in an abstract for the 2017 San Antonio Breast Cancer Symposium³⁰;

results of the primary (*i.e.* safety of the combination, and ORR) and secondary (*i.e.* PFS, duration of response, and OS) endpoints have not been published in public databases.

From our review on trastuzumab clinical trials, we observed that the ORR for trastuzumab monotherapy was below 30% with the majority of the patients not achieving either PR or CR. As anticipated, combination regimens with trastuzumab demonstrated greater ORR of above 50% with 25-50% of the patients achieving pCR *i.e.* free from invasive disease in the breast and in the axillary lymph nodes at the completion of neoadjuvant treatment.

Pertuzumab

Pertuzumab (Perjeta) is a newer generation of anti-HER2 mAb for the treatment of HER2-positive MBC and received FDA approval in 2012. Pertuzumab serves as a HER dimerization inhibitor by binding the dimerization arm of HER2 at subdomain II, thereby reducing HER2 intracellular signaling by preventing HER2 from forming heterodimers with other HER receptors and EGFR³¹⁻³³. As subdomain II does not overlap with other domains or epitopes that bind trastuzumab (subdomain IV), the combination of trastuzumab and pertuzumab could enhance the blockage of HER2-mediated signal transduction³⁴

Pertuzumab monotherapy

In a phase II trial involving HER2-positive locally advanced and MBC patients (n=29) receiving pertuzumab with prior trastuzumab-based therapy, the ORR and CBR were 3.4% and 10.3%, respectively, with PFS of only 7.1 weeks³⁵. Seventeen patients with disease progression continued to receive pertuzumab with the addition of trastuzumab, and the ORR and CBR were 17.6% and 41.2%, respectively, with improved PFS of 17.4 weeks³⁵. The clinical trial showed that pertuzumab monotherapy had lower efficacy compared to addition of trastuzumab.

Pertuzumab in combination with chemotherapy

In a randomized, open-label phase II clinical trial (NeoSphere) on patients with HER2-positive breast cancer, the patients were subgrouped to receive different treatment regimens as follows: (i) Trastuzumab-docetaxel (group A; n=107); (ii) Pertuzumab-trastuzumab-docetaxel (group B; n=107); (iii) Pertuzumab-trastuzumab (group C; n=107); (iv) Pertuzumab-docetaxel (group D; n=96)³⁶. Patients in group B had the highest and significantly improved pCR of 45.8% (n=49) compared with 29.0% in group A (n=31; $p=0.0141$), while groups C and D achieved lower pCR of 16.8% (n=18) and 24.0% (n=23), respectively³⁶. The best combination in this study was group B (pertuzumab-trastuzumab-docetaxel). The NeoSphere trial that involved large number of patients (n=417) with highly encouraging results led to the accelerated approval of pertuzumab by

the FDA in September 2013 for the neoadjuvant treatment of high-risk HER2-positive breast cancer as a first-line therapy combined with trastuzumab and chemotherapy.

Other clinical trials have since attempted to examine the efficacy of pertuzumab-trastuzumab combination with other chemotherapy regimens. TRYPHAENA phase II trial involved HER2-positive early breast cancer patients that were randomized to receive six neoadjuvant cycles as follows: (i) Arm A (n=72) receiving 5-fluorouracil, epirubicin, cyclophosphamide (FEC) followed by docetaxel (T), with trastuzumab (H) and pertuzumab (P) (FEC+H+P×3→T+H+P×3); (ii) Arm B (n=75) receiving FEC followed by T+H+P (FEC×3→T+H+P×3); (iii) Arm C receiving T, carboplatin, H with P (TCH+P×6)³⁷. The pCR achieved was 61.6%, 57.3% and 66.2% in Arm A, B and C, respectively. Clinical CR was achieved by 50.7% (Arm A), 28.0% (Arm B) and 40.3% (Arm C).

In a phase II trial, patients with HER2-positive MBC with 0-1 prior treatments (n=51 and n=18 treated in first- and second-line metastatic settings, respectively) were selected. They received treatment combination of paclitaxel weekly, and trastuzumab and pertuzumab every three weeks³⁸. The median OS was 44 months (95% CI: 37.5-not reached [NR]) overall, and 44 months (95% CI: 38.3-NR) and 37.5 months (95% CI: 30.3-NR) for patients with 0 and 1 prior metastatic treatment, respectively. Median PFS was 21.4 months (95% CI: 14.1-NR) overall, and 25.7 months (95% CI: 14.1-NR) and 16.9 months (95% CI: 8.5-NR) for patients with 0 and 1 prior treatment, respectively. Favorable OS and PFS were achieved when paclitaxel was added weekly into trastuzumab and pertuzumab regimen³⁸.

The VELVET phase II trial assessed the efficacy and safety of pertuzumab, trastuzumab and vinorelbine combination in patients with HER2-positive locally advanced or MBC (n=106)³⁹. Encouraging results were shown where the ORR was 74.2% (95% CI:63.8-82.9%) while the median PFS was 14.3 months (95% CI:11.2-17.5 months). Another phase II trial was conducted on HER2-positive advanced breast cancer patients (n=30) pretreated with taxanes and trastuzumab⁴⁰. The patients were treated with eribulin in combination with pertuzumab and trastuzumab. The ORR was 34.8% (n=23), and median PFS was 42.6 weeks (n=30, 95% CI: 20.3-51.9 weeks). Combination of eribulin with anti-HER2 therapy (pertuzumab-trastuzumab) was well tolerated in heavily pretreated patients.

A recent (2018) multicentre, open-label, randomized, phase II trial on HER2-positive MBC elderly patients without previous chemotherapy for metastatic disease showed that dual HER2 blockade with trastuzumab and pertuzumab (n=39) had lower efficacy than dual HER2 blockade plus metronomic oral cyclophosphamide

as follows: PFS at 6 months was 46.2% vs 73.4%; at median follow-up of 20.7 months, median PFS was 5.6 months vs 12.7 months⁴¹. The authors concluded that trastuzumab and pertuzumab plus metronomic oral cyclophosphamide increased median PFS by seven months with tolerable safety profile, and suggested that this regimen can replace the need for taxane chemotherapy in elderly HER2-positive MBC patients.

In a phase III trial (CLEOPATRA), 808 patients with HER2-positive MBC were assigned to receive pertuzumab-trastuzumab-docetaxel (pertuzumab group) or placebo-trastuzumab-docetaxel (control group) as the first-line treatment⁴². The median PFS was significantly greater in the pertuzumab group (18.5 months) compared with the control group (12.4 months) ($p<0.001$), and the median OS was significantly improved to 56.5 months compared with 40.8 months in the control group ($p<0.001$)⁴². This trial further established the improved clinical benefits of the pertuzumab-trastuzumab-docetaxel combination regimen in a phase III setting, consistent with the results shown by the phase II NeoSphere trial.

In another phase III trial (PHEREXA), trastuzumab plus capecitabine with or without pertuzumab was given to patients with HER2-positive MBC who had disease progression during or after trastuzumab-based therapy and received prior a taxane⁴³. The patients were divided into arm A (n=224; trastuzumab plus capecitabine) and arm B (n=228; pertuzumab plus trastuzumab and capecitabine). Median independent review facility-assessed (IRF) PFS was 28.6 and 25.3 months for arm A and B, respectively. The final OS was 28.1 months (arm A) vs 37.3 months (arm B). The addition of pertuzumab to trastuzumab and capecitabine did not significantly improve independent review facility-assessed (IRF) PFS^{43,44}.

The APHINITY phase III trial aimed to investigate whether addition of pertuzumab to adjuvant trastuzumab and chemotherapy was efficacious in HER2-positive early breast cancer⁴⁵. The study randomly assigned patients with node-positive or high-risk node-negative HER2-positive breast cancer to receive either pertuzumab (n=2,400) or placebo (n=2,405) with standard adjuvant chemotherapy plus one year of treatment with trastuzumab. The addition of pertuzumab improved the three-year iDFS (94.1%) compared with the placebo group (93.2%). This represented an 18% reduction in the risk of developing invasive disease or death (HR=0.81; 95% CI: 0.66-1.00; $p=0.045$). Furthermore, the four-year iDFS were 92.3% vs 90.6%, and invasive-disease events were observed in 7.1% (n=171) in the pertuzumab group which was lower than the 8.7% in the placebo group (n=210). APHINITY is one of the pivotal clinical trials that led to the FDA approval (in December 2017) of pertuzumab in combination with trastuzumab for adjuvant treatment in HER2-

positive early breast cancer patients at high risk of recurrence.

In a neoadjuvant phase four study (NBRST), HER2-positive breast cancer patients (n=297) were enrolled to receive neoadjuvant chemotherapy (NCT) and underwent treatment with trastuzumab (T), or trastuzumab and pertuzumab (T/P)⁴⁶. Amongst the patients, 60% received NCT-T and the remaining 40% received NCT-T/P. Patients treated with NCT-T/P had higher pCR rates than those treated with trastuzumab alone. Addition of pertuzumab to trastuzumab significantly improved the pCR rate in HER2-positive/ER-positive patients (but not HER2-positive/ER-negative patients) where 33 of 111 patients (29.7%) reached pCR with trastuzumab (95% CI: 22.0-38.8%) versus 33 of 73 patients (48%) with trastuzumab plus pertuzumab (95% CI: 36.9-59.2%) ($p=0.0188$).

Pertuzumab in combination with chemotherapy-free regimens

In a phase II trial, the efficacy and safety profile of the pertuzumab-trastuzumab combination was assessed in patients with HER2-positive breast cancer (n=66) who had disease progression during prior trastuzumab-based therapy⁴⁷. The ORR was 24.2%, CBR was 50% (CR: 7.6%; n=5, PR: 16.7%; n=11), and SD of six months was 25.8% (n=17). Median PFS was 5.5 months, and this combination was well tolerated. In a recent phase II trial (NAPHER2) of multi-agents regimen targeting ER (fulvestrant), HER2 (trastuzumab and pertuzumab), and RB1 (palbociclib, an inhibitor of CDK4/6 approved for treatment of breast cancer)^{48,49} in HER2-positive and ER-positive breast cancer (n=30), a clinical ORR immediately before surgery was achieved by 97% (n=29) of the patients⁵⁰. At surgery, 27% (n=8) patients had a pCR in breast and axillary nodes. These encouraging results have prompted the authors to currently investigate whether HER2-ER-RB1 triple block is effective in ER-positive breast cancer patients without HER2 amplification or overexpression.

Trastuzumab emtansine (T-DM1)

Trastuzumab emtansine or T-DM1 (Kadcyla) was the first ADC approved for cancer therapy in 2013. T-DM1 was developed to improve the efficacy of breast cancer treatment in patients with previously treated HER2-positive MBC and those who developed trastuzumab resistance⁵¹. The HER2-targeting ADC consists of the conjugation between trastuzumab with the cytotoxic agent emtansine (DM1, derivative of maytansine) via a non-reducible thioether linker⁵². The ADC linker tethers the antibody to a cytotoxic agent which enables stable circulation of the cytotoxin in the form of a prodrug⁵³. The functions of the linker include modulation of cytotoxin release in tumor cells, overcoming multidrug resistance, and enhancing tumor penetration.

T-DM1 binds to HER2-expressing cells with the common affinity of trastuzumab and selectively delivers DM1 to HER2-positive tumor cells via endocytosis, thus maximizing the therapeutic potential of DM1 with minimal off-target effects^{31,54}. DM1-containing metabolites eventually inhibit microtubule assembly, causing apoptosis in HER2-overexpressed cancer cells^{52,55}. It also facilitates antibody-dependent cellular cytotoxicity (ADCC), inhibits HER2 extracellular domain shedding, and inhibits the PI3K signaling pathway^{54,56}.

T-DM1 monotherapy

Three phase I studies had demonstrated the therapeutic potential and tolerability of T-DM1 monotherapy, and established the optimal dosage of 3.6mg/kg every 3 weeks⁵⁷⁻⁵⁹. A single-arm phase II study (TDM4258g) on HER2-positive MBC patients (n=112) who received prior HER2-targeted therapies or chemotherapy showed that patients treated with the established 3.6mg/kg of T-DM1 every 3 weeks had median PFS of 4.6 months (95% CI: 3.9-8.6 months), and 25.9% (n=29) of the patients achieved ORR, 37.5% (n=42) patients achieving objective responses including 3.6% (n=4) experienced CR⁶⁰.

In a pivotal phase III trial (EMILIA) assessing HER2-positive advanced breast cancer previously treated with trastuzumab and a taxane (n=991), the patients were given the standard 3.6mg/kg every 3 weeks with dose delays, reductions or discontinuations due to toxic effects were also conducted⁶¹. The median PFS and OS with T-DM1 (n=495) was significantly longer than the group receiving lapatinib plus capecitabine (L+C; n=496) (median PFS: 9.6 vs 6.4 months, $p<0.001$; median OS: 30.9 vs 25.1 months, $p<0.001$). The ORR was also significantly higher in T-DM1 than L+C (43.6% vs 30.8%; $p<0.001$), while the rates of grade ≥ 3 adverse events (AEs) were higher in L+C than T-DM1 (57% vs 41%). As the trial reported superior clinical benefits with less toxicity, it led to the approval of T-DM1 use by FDA in February 2013.

The results of improved OS with T-DM1 in the EMILIA trial were also consistent with those of another phase III (TH3RESA) clinical trial conducted on patients with HER2-positive advanced breast cancer who were previously treated with trastuzumab, lapatinib and a taxane⁵⁴. Patients were assigned to receive T-DM1 (n=404) versus treatment of physician's choice (n=198), and OS was significantly longer in T-DM1 (22.7 months) versus treatment of physician's choice (15.8 months; $p=0.0007$). The favorable safety profile was also maintained despite the mean treatment duration with T-DM1 was almost twice as long compared with treatments of physician's choice.

T-DM1 in combination with chemotherapy

A phase II trial evaluated the safety of T-DM1 plus paclitaxel combination with or without

pertuzumab in HER2-positive advanced breast cancer patients (n=44)⁶². A total of 51.2% received ≥ 12 paclitaxel doses within 15 weeks. Among the 42 patients with measurable disease, ORR was 50% and the CBR was 56.8%. No pharmacokinetic interactions were observed between T-DM1 and paclitaxel combination. A subsequent phase Ib/IIa study assessed the feasibility of T-DM1 plus docetaxel in patients with HER2-positive MBC (n=25) and T-DM1 plus docetaxel with or without pertuzumab in patients with HER2-positive locally advanced breast cancer (LABC; part 2; n=73)⁶³. The resulting MTD for T-DM1 was 3.6mg/kg while docetaxel was 60mg/m². In MBC patients, the ORR was 80% with median PFS of 13.8 months while the pCR rate in LABC patients was 60.3%, while drug-drug interaction between T-DM1 and docetaxel was of low risk according to pharmacokinetic analyses. However, the authors reported that almost half of the patients had AEs that necessitated dose reductions in these T-DM1 combination regimens.

T-DM1 in combination with chemotherapy-free regimens

In a phase II trial of T-DM1 and pertuzumab combination treatment in patients with HER2-positive MBC⁶⁴, 21 patients in the first-line setting and 43 patients in second-line setting (advanced MBC) were enrolled. The ORR and median PFS was 57% and 7.7 months for first-line patients, while 33% and 5.5 months for advanced MBC, respectively. The authors concluded that T-DM1 and pertuzumab can be combined at full doses without unexpected toxicities.

Phase III trial (MARIANNE) was conducted on HER2-positive advanced breast cancer patients (n=1,095) with no prior therapy for advanced disease⁶⁵. The patients were randomly assigned to receive T-DM1 plus placebo, T-DM1 plus pertuzumab, or trastuzumab plus a taxane (control group). T-DM1 in combination with other agents showed less clinical benefit than the control group but better tolerability and lesser side effects. The ORR was 59.7% (T-DM1 plus placebo), 64.2% (T-DM1 plus pertuzumab), and 67.9% (control group).

The KRISTINE clinical trial (phase III) was conducted by assigning patients with HER2-positive breast cancer stage II-III to receive either neoadjuvant treatment with T-DM1 plus pertuzumab (n=223) or docetaxel, carboplatin, trastuzumab plus pertuzumab (DCTP; n=221)⁶⁶. The pCR of 44.4% was lower in the T-DM1 group (n=9) vs 55.7% (n=123) in the DCTP group ($p=0.016$). However, patients in the DCTP group experienced more frequent and serious AEs than in the T-DM1 group, indicating that T-DM1 plus pertuzumab alone represents a potential neoadjuvant treatment to limit the occurrence of serious AEs. Summary of the phase II/III trials discussed in this paper are presented in Table 1A

and Table 1B (trastuzumab), Table 2A and Table 2B (pertuzumab), and, Table 3A and Table 3B (T-DM1). Ongoing phase II and III clinical trials of trastuzumab, pertuzumab and T-DM1 not discussed in this review are presented in Table 4.

Chemotherapy of choice for anti-HER2 therapeutic antibodies

Several phase II and III trials have demonstrated that pertuzumab plus trastuzumab in combination with chemotherapy regimens confer enhanced clinical outcomes compared with pertuzumab plus trastuzumab alone, or antibody monotherapy, for metastatic or advanced HER2-positive breast cancer patients (Tables 1 and 2). Moreover, multiple clinical trials have shown that although T-DM1 plus pertuzumab without chemotherapy has better safety profile, the combination confers lower efficacy than chemotherapy-containing regimens (Table 3). Therefore in this section, we suggest the optimal chemotherapy of choice for each of the three anti-HER2 therapeutic antibodies. Studies involving treatment-naïve HER2-positive breast cancer patients only were included in the comparison and discussion. This was due to different regimens were used in pre-treatment of HER2-positive breast cancer patients and such heterogeneity hindered direct comparisons (Tables 1-3). Trastuzumab plus paclitaxel was the commonly used chemotherapy-containing regimen for MBC or stage II/III HER2 positive treatment-naïve breast cancer patients²²⁻²⁴. In these phase II and III studies, trastuzumab and paclitaxel combined with either carboplatin²³ or lapatinib²⁴ showed improvements in the ORR or pCR. For trastuzumab in combination with chemotherapy-free regimen, trastuzumab plus lapatinib also showed markedly higher pCR (51.3%) compared with lapatinib (24.7%) or trastuzumab alone (29.5%)²⁸. These suggest that combination of trastuzumab with lapatinib, with or without paclitaxel, represents the optimal combination regimen containing trastuzumab.

In terms of pertuzumab, dual anti-HER2 therapy (pertuzumab and trastuzumab) combined with chemotherapy has shown improved efficacy compared with either antibody alone in terms of pCR^{36,46}, PFS^{41,42}, and OS⁴²⁻⁴⁴. In treatment-naïve breast cancer patients treated with trastuzumab and pertuzumab, combination with chemotherapies including 5-fluorouracil, epirubicin and cyclophosphamide followed by docetaxel and both antibodies yielded superior pCR (61.6%) compared with other chemotherapy-containing regimens such as docetaxel only³⁶ and neoadjuvant chemotherapy⁴⁶. In terms of pertuzumab in combination with chemotherapy-free regimen, only one regimen (pertuzumab plus trastuzumab, palbociclib and fulvestrant) has been assessed in treatment-naïve HER2-positive breast cancer patients with promising ORR and pCR⁵⁰.

Table 1A: Summary of phase II/III trials of trastuzumab discussed in this review

Antibody	Trial ID/ Authors	Phase	Patient Population	Pre-treatment	Treatment	Outcomes
Trastuzumab monotherapy	Baselga <i>et al.</i> ¹⁶	II	HER2-positive MBC (n=43)	No	Trastuzumab monotherapy	ORR: 11%; CR: 2.3%
	Cobleigh <i>et al.</i> ¹⁷	II	HER2-positive MBC (n=222)	No	Trastuzumab monotherapy	CR: 3.6%; PR: 11.7%; ORR: 15%
	Vogel <i>et al.</i> ¹⁸	II	HER2-overexpressing MBC (n=114)	No	Trastuzumab monotherapy	ORR: 26%; CR: 6.1%; PR: 20.2%; Response rate: 35%; CBR: 48%
	Baselga <i>et al.</i> ¹⁹	II	HER2-positive MBC (n=105)	No	Trastuzumab monotherapy	ORR: 19%; CR: 1.9%; PR: 17.1%; CBR: 33% and median time to progression: 3.4 months
	NCT00045032 (HERA) ²⁰	III	HER2-positive early breast cancer (n=5,102)	Adjuvant chemotherapy	1 year of trastuzumab/ 2 years of trastuzumab/ observation	10-year DFS: 69% vs 69% vs 63%
Trastuzumab in combination with chemotherapy	NCT00542451 ²¹	II	HER2-positive breast cancer (n=406)	No	Trastuzumab + paclitaxel	iDFS: 98.7%
	Robert <i>et al.</i> ²³	II	HER2-overexpressing MBC (n=196)	No	Trastuzumab + paclitaxel + carboplatin/ trastuzumab + paclitaxel	ORR: 52% vs 36%; Median PFS: 10.7 months vs 7.1 months
	NCT00915018 (NEfERT-T) ²²	II	Recurrent and/or HER2-positive MBC (n=479)	No	Trastuzumab + paclitaxel/ neratinib + trastuzumab	ORR: 77.6% vs 74.8%; CBR: 85.2% vs 88.4%; Median PFS: 12.9 months vs 12.9 months
	NCT00770809 (CALGB40601) ²⁴	III	Stage II to III HER2-positive breast cancer (n=305)	No	Paclitaxel + trastuzumab/ paclitaxel + trastuzumab + lapatinib/ paclitaxel + lapatinib	pCR: 46% vs 56% vs 32%
	NCT01125566 (LUX-Breast 1) ²⁵	III	HER2-overexpressing MBC (n=508)	Trastuzumab	Afatinib + vinorelbine/ trastuzumab + vinorelbine	Median PFS: 5.5 months vs 5.6 months

CBR: Clinical benefit rate, CR: Complete response, DFS: Disease-free survival, HER2: Human epidermal growth factor receptor 2, iDFS: Invasive disease-free survival, MBC: Metastatic breast cancer, ORR: Objective response rate, pCR: Pathological complete response, PFS: Progression-free survival, PR: Partial response

Table 1B: Summary of phase II/III trials of trastuzumab discussed in this review

Antibody	Trial ID/ Authors	Phase	Patient Population	Pre-treatment	Treatment	Outcomes
Trastuzumab in combination with chemotherapy-free regimen	Pistilli <i>et al.</i> ²⁷	II	HER2-positive advanced breast cancer patients (n=50)	HER2-targeted therapy, chemotherapy	Buparlisib + trastuzumab	ORR: 10%
	NCT00553358 (NeoALTTO) ²⁸	III	HER2-positive primary breast cancer (n=455)	No	Lapatinib/ trastuzumab monotherapy/ trastuzumab + lapatinib	pCR: 24.7% vs 29.5% vs 51.3%
	Johnston <i>et al.</i> (ALTERNA-TIVE) ²⁹	III	HER2-positive/HR-positive MBC (n=355)	Endocrine treatment and prior neo(adjuvant)/ first-line TRAS plus chemotherapy	Lapatinib + trastuzumab (TRAS) + aromatase inhibitor (AI)/ TRAS + AI/ lapatinib + AI	Median PFS: 11 months vs 8.3 months vs 5.7 months

CBR: Clinical benefit rate, CR: Complete response, DFS: Disease-free survival, HER2: Human epidermal growth factor receptor 2, iDFS: Invasive disease-free survival, MBC: Metastatic breast cancer, ORR: Objective response rate, pCR: Pathological complete response, PFS: Progression-free survival, PR: Partial response

Table 2A: Summary of phase II/III trials of pertuzumab discussed in this review

Antibody	Trial ID/ Authors	Phase	Patient Population	Pre-treatment	Treatment	Outcomes
Pertuzumab monotherapy	NCT00301899 ³⁵	II	HER2-positive advanced or MBC (n=29)	Trastuzumab based therapy	Pertuzumab monotherapy/ pertuzumab + trastuzumab	ORR: 3.4% vs 17.6% CBR: 10.3% vs 41.2% PFS: 7.1 weeks vs 17.4 weeks
Pertuzumab in combination with chemotherapy	NCT00545688 (NeoSphere) ³⁶	II	HER2-positive breast cancer (n=417)	No	Trastuzumab + docetaxel/ pertuzumab + trastuzumab + docetaxel/ pertuzumab + trastuzumab/ pertuzumab + docetaxel	pCR: 29.0% vs 45.8% vs 16.8% vs 24.0%
	Schneeweiss <i>et al.</i> (TRYPHAENA) ³⁷	II	HER2-positive early breast cancer (n=225)	No	5-fluorouracil, epirubicin, cyclophosphamide [FEC] + trastuzumab [H] + pertuzumab [P] ×3 → docetaxel [T] + H + P ×3/ FEC ×3 → T + H + P ×3/ T + carboplatin + H [TCH] + P ×6)	pCR: 61.6% vs 57.3% vs 66.2% ORR: 89.6%-94.7% CR: 50.7% vs 28.0% vs 40.3%
	Smyth <i>et al.</i> ³⁸	II	HER2-positive MBC (n=69)	Adjuvant trastuzumab, lapatinib, ET, chemotherapy	Pertuzumab + trastuzumab + paclitaxel	Median OS: 44 months Median PFS: 21.4 months
	NCT01565083 (VELVET) ³⁹	II	HER2-positive locally advanced or MBC (n=89)	Taxane, anthracycline, trastuzumab, bevacizumab	Pertuzumab + trastuzumab + vinorelbine	ORR: 74.2% Median PFS: 14.3 months
	UMIN000012375 ⁴⁰	II	HER2-positive advanced breast cancer patients (n=30)	Taxanes and trastuzumab	Eribulin + pertuzumab + trastuzumab.	ORR: 34.8% Median PFS: 42.6 weeks

CBR: Clinical benefit rate, CR: Complete response, DFS: Disease-free survival, HER2: Human epidermal growth factor receptor 2, iDFS: Invasive disease-free survival, IRF PFS: Independent review facility-assessed progression-free survival, MBC: Metastatic breast cancer, ORR: Objective response rate, pCR: Pathological complete response, PFS: Progression-free survival, PR: Partial response, SD: Stable disease

Table 2B: Summary of phase II/III trials of pertuzumab discussed in this review

Antibody	Trial ID/ Authors	Phase	Patient Population	Pre-treatment	Treatment	Outcomes
Pertuzumab in combination with chemotherapy	NCT01597414 ⁴¹	III	HER2-positive MBC (n=39)	Yes	Trastuzumab + pertuzumab/ Trastuzumab + pertuzumab + metronomic oral cyclophosphamide	Median PFS was 5.6 months vs 12.7 months
	NCT01026142 (PHEREXA) ^{43,44}	III	HER2-positive MBC (n=452)	Trastuzumab-based therapy and taxane	Trastuzumab + capecitabine/ pertuzumab + trastuzumab + capecitabine	IRF PFS: 28.6 months vs 25.3 months OS: 28.1 months vs 37.3 months
	NCT00567190 (CLEOPATRA) ⁴²	III	HER2-positive MBC (n=808)	Trastuzumab	Pertuzumab + trastuzumab + docetaxel/ placebo + trastuzumab + docetaxel	PFS: 18.5 months vs 12.4 months Median OS: 56.5 months vs 40.8 months
	NCT01358877 (APHINITY) ⁴⁵	III	HER2-positive breast cancer (n=4,805)	No	Pertuzumab + trastuzumab/ pertuzumab + placebo	3-year rate of iDFS: 94.1% vs 93.2% Invasive-disease events: 7.1% vs 8.7%
	NCT01479101 (NBRST) ⁴⁶	IV	HER2-positive breast cancer patients (n=297)	No	Neoadjuvant chemotherapy (NCT) + trastuzumab / NCT+ trastuzumab + pertuzumab	pCR: 29.7% vs 48.0%
Pertuzumab in combination with chemotherapy-free regimen	NCT02530424 (NA-PHER2) ⁵⁰	II	HER2-positive breast cancer (n=30)	No	Trastuzumab + pertuzumab + palbociclib + fulvestrant	ORR (before surgery): 97%; pCR (at surgery): 27%
	Baselga <i>et al.</i> ⁴⁷	II	HER2-positive breast cancer (n=66)	Trastuzumab-based therapy	Pertuzumab + trastuzumab	ORR: 24.2%; CBR: 50%; CR: 7.6%; PR:16.7%; SD: 25.8%

CBR: Clinical benefit rate, CR: Complete response, DFS: Disease-free survival, HER2: Human epidermal growth factor receptor 2, iDFS: Invasive disease-free survival, IRF PFS: Independent review facility-assessed progression-free survival, MBC: Metastatic breast cancer, ORR: Objective response rate, pCR: Pathological complete response, PFS: Progression-free survival, PR: Partial response, SD: Stable disease

Table 3A: Summary of phase II/III trials of T-DM1 discussed in this review

Antibody	Trial ID/ Authors	Phase	Patient Population	Pre-treatment	Treatment	Outcomes
T-DM1 monotherapy	NCT00509769 (TDM4258g) ⁶⁰	II	HER2-positive MBC (n=112)	HER2-targeted therapies or chemotherapy	T-DM1 monotherapy	ORR: 25.9%; Median PFS: 4.6 months; objective responses: 37.5%; CR: 3.6%
	NCT00679341 (TDM4450) ⁶⁹	II	HER2-positive MBC (n=137)	Taxane, trastuzumab, anthracycline	T-DM1 monotherapy/ trastuzumab + docetaxel	Median PFS: 14.2 months vs 9.2 months; ORR: 64.2% vs 58.0%
	Krop <i>et al.</i> ⁷⁰	II	HER2-positive MBC (n=110)	Trastuzumab, lapatinib, an anthracycline, a taxane, and capecitabine	T-DM1 monotherapy	ORR: 34.5%; CBR: 48.2%; median PFS: 6.9 months;
	Kashiwaba <i>et al.</i> (JO22997) ⁷¹	II	HER2-positive inoperable locally advanced/recurrent or MBC (n=73)	Chemotherapy regimen and trastuzumab	T-DM1 monotherapy	ORR: 38.4%; Median PFS: 5.6 months; Median OS: 30.5 months
	NCT01745965 (ADAPT) ⁷²	II	HER2-positive/HR- positive early breast cancer patients (n=375)	No	T-DM1/ T-DM1 + endocrine therapy / trastuzumab + endocrine therapy	pCR: 41.0% vs 41.5% vs 15.1%
	NCT01419197 (TH3RESA) ⁵⁴	III	HER2-positive advanced breast cancer (n=602)	Trastuzumab, lapatinib and a taxane	T-DM1/ physician's choice	OS: 22.7 months vs 15.8 months
	NCT00829166 (EMILIA) ⁶¹	III	HER2-positive advanced breast cancer (n=991)	Trastuzumab and a taxane	T-DM1/ lapatinib + capecitabine	PFS: 9.6 months vs 6.4 months OS: 30.9 months vs 25.1 months ORR: 43.6% vs 30.8%

CBR: Clinical benefit rate, CR: Complete response, DFS: Disease-free survival, HER2: Human epidermal growth factor receptor 2, iDFS: Invasive

Table 3B: Summary of phase II/III trials of T-DM1 discussed in this review

Antibody	Trial ID/ Authors	Phase	Patient Population	Pre-treatment	Treatment	Outcomes
T-DM1 in combination with chemotherapy	NCT00951665 ⁶²	II	HER2-positive advanced breast cancer patients (n=44)	Taxane, trastuzumab, anthracycline, lapatinib	T-DM1 + paclitaxel + pertuzumab	ORR: 50%; CBR: 56.8 %
	NCT00934856 ⁶³	II	HER2-positive MBC and locally advanced breast cancer (n=98)	Taxane, trastuzumab	T-DM1 + docetaxel + pertuzumab	ORR: 80%; median PFS: 13.8 months; pCR: 60.3%
T-DM1 in combination with chemotherapy-free regimen	NCT00875979 ⁶⁴	II	HER2-positive MBC (n=64)	Taxane, trastuzumab, anthracycline, lapatinib, capecitabine	T-DM1 + pertuzumab	ORR: 57% (first line) vs 33% (second line) PFS: 7.7 months (first line) vs 5.5 months (second line)
	NCT01120184 (MARIANNE) ⁶⁵	III	HER2-positive, advanced breast cancer patients (n=1,095)	Taxane, trastuzumab, anthracycline	T-DM1 + placebo/ T-DM1 + pertuzumab/ trastuzumab + a taxane (control)	PFS: 14.1 months vs 15.2 months vs 13.7 months ORR: 59.7% vs 64.2% vs 67.9%
	NCT02131064 (KRISTINE) ⁶⁶	III	HER2-positive breast cancer stage II III (n=444)	No	T-DM1 + pertuzumab/ docetaxel + carboplatin + trastuzumab + pertuzumab	pCR: 44.4% vs 55.7%

CBR: Clinical benefit rate, CR: Complete response, DFS: Disease-free survival, HER2: Human epidermal growth factor receptor 2, iDFS: Invasive

Table 4: Ongoing clinical trials of anti-HER2 therapeutic antibodies

Antibody	Trial	Phase	Patient Population	Treatment	Primary Completion
Trastuzumab	NCT02614794 (HER2CLIMB) ⁷³	II	Locally advanced or HER2-positive MBC (n=480)	Tucatinib / Placebo + capecitabine + trastuzumab	July 2021
	NCT02625441 (BOLD-1) ⁷⁴	III	Early HER2-positive breast cancer (n=1,366)	Trastuzumab + pertuzumab + docetaxel	June 2023
	NCT01810393 ⁷⁵	III	HER2-positive MBC (n=114)	Trastuzumab / participant preference for subcutaneous	August 2019
	NCT01785420 ⁷⁶	III	HER2-neu positive operable breast cancer (n=1,100)	Trastuzumab + placebo	February 2021
Pertuzumab	NCT02536339 (PATRICIA) ⁷⁷	II	HER2-positive MBC with central nervous system progression post- radiotherapy (n=40)	Pertuzumab + high-dose trastuzumab	March 2020
	NCT02514681 (PRECIOUS) ⁷⁸	III	HER2-positive advanced breast cancer (n=370)	Pertuzumab + trastuzumab + chemotherapy	July 2019
Transtuzumab emtansine (T- DM1)	NCT03084939 ⁶⁷	III	HER2-positive locally advanced or MBC (n=350)	T-DM1/ lapatinib + capecitabine	October 2019
	NCT01772472 (KATHERINE) ⁷⁹	III	HER2-positive breast cancer (n=1,487)	T-DM1/ Trastuzumab	April 2023
	NCT01966471 ⁶⁸	III	Operable HER2-positive primary breast cancer (n=1,846)	T-DM1 + pertuzumab + anthracyclines/ trastuzumab + pertuzumab + a taxane	January 2024

HER2: Human epidermal growth factor receptor 2, MBC: Metastatic breast cancer, T-DM1: Trastuzumab emtansine

For T-DM1, none of the phase II/III clinical trials have assessed on treatment-naïve HER2-positive breast cancer patients in combination with chemotherapy. Nonetheless, T-DM1 in combination with pertuzumab and docetaxel might represent the ideal chemotherapy-containing regimen where the ORR achieved was high (80%)⁶³ compared with another chemotherapy-containing regimen (T-DM1 plus pertuzumab and paclitaxel; ORR: 50%)⁶². In terms of T-DM1 in combination with chemotherapy-free regimen, the phase III KRISTINE study has demonstrated that T-DM1 plus pertuzumab showed lower pCR than chemotherapy-containing regimen⁶⁶.

CONCLUSION

Ongoing phase III clinical trials are assessing the combination of T-DM1 with capecitabine in HER2-positive locally advanced or MBC (n=350; NCT03084939)⁶⁷, or T-DM1 plus pertuzumab in combination with anthracyclines in operable HER2-positive breast cancer patients (n=1,86; NCT01966471)⁶⁸. Taken together, these indicate that improved outcome is attributable to treatment selection in combination with anti-HER2 antibodies instead of replacing chemotherapy altogether with current line of anti-HER2 therapeutic antibodies. Finally, large clinical trials of anti-HER2 antibodies in early HER2-positive or operable breast cancer are currently underway.

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Conflict of interest statement

All authors declare that there are no conflicts of interest.

Authors' contributions

K.K.W. and S.M.N.H. conceived and designed the manuscript, conducted literature searches, made the figures, prepared the tables, and wrote the manuscript. A.D.P., F.A.H. and M.M.Y. edited and revised the manuscript. All authors read and approved the final manuscript.

Conflict of interest

The authors declare no potential conflict of interest.

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