Standard-of-Care Treatment for HER2+ Metastatic Breast Cancer and Emerging Therapeutic Options

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Breast Cancer: Basic and Clinical Research
Volume 18: 1–23

DOI: 10.1177/11782234241234418

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ABSTRACT: Prior to the advent of the HER2-targeted monoclonal antibody trastuzumab, HER2+ breast cancer (BC) was considered an aggressive disease with a poor prognosis. Over the past 25 years, innovations in molecular biology, pathology, and early therapeutics have transformed the treatment landscape. With the advent of multiple HER2-directed therapies, there have been immense improvements in oncological outcomes in both adjuvant and metastatic settings. Currently, 8 HER2-targeted therapies are approved by the Food and Drug Administration (FDA) for the treatment of early-stage and/or advanced/metastatic disease. Nonetheless, approximately 25% of patients develop recurrent disease or metastasis after HER2-targeted therapy and most patients with HER2+ metastatic breast cancer (MBC) die from their disease. Given the many mechanisms of resistance to HER2-directed therapy, there is a pressing need to further personalize care for patients with HER2+ MBC, by the identification of reliable predictive biomarkers, and the development of novel therapies and combination regimens to overcome therapeutic resistance. Of particular interest are established and novel antibody-drug conjugates, as well as other novel therapeutics and multifaceted approaches to harness the immune system (checkpoint inhibitors, bispecific antibodies, and vaccine therapy). Herein, we discuss standard-of-care treatment of HER2+ MBC, including the management of breast cancer brain metastases (BCBM). Furthermore, we highlight novel treatment approaches for HER2+ MBC, including endeavors to personalize therapy, and discuss ongoing controversies and challenges.

KEYWORDS: HER2+ breast cancer, metastatic breast cancer, brain metastases, biomarkers, novel therapies

RECEIVED: July 15, 2023. **ACCEPTED:** January 30, 2024.

TYPE: Current and future prospective of breast cancer treatment and research - Review

FUNDING: The author(s) received no financial support for the research, authorship, and/or publication of this article.

COMPETING INTERESTS: The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

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Introduction

In 2023, approximately 300 590 persons were diagnosed with metastatic breast cancer (MBC) in the United States,[1] and approximately 15% to 20% were human epidermal growth factor receptor 2 (HER2) positive.[2] This breast cancer (BC) subtype is characterized by overexpression of HER2, a ligand orphan receptor tyrosine kinase that forms heterodimers with other HER family members (HER1, HER3, and HER4), amplifying their signal.[3] Human epidermal growth factor receptors are composed of an extracellular ligand-binding domain, a transmembrane domain, and an intracellular tyrosine kinase domain. When external ligands bind to HER proteins, homo- or heterodimerization of the receptor occurs, activating downstream signaling (including the mitogen-activated protein kinase [MAPK] and phosphatidylinositol-3-OH kinase [PI3K] pathways), promoting cell division and growth while inhibiting apoptosis (Figure 1). Overexpression or amplification of the HER2 oncogene plays an important role in development and progression of this BC subtype and correlates with chemotherapy resistance and aggressive disease.[4] Per the American Society of Clinical Oncology–College of American Pathologists guidelines, HER2-positivity is defined as tumors that exhibit 3+ positive staining via immunohistochemistry (IHC) in ⩾10% of tumor cells, or tumors with 2+ or equivocal IHC staining where HER2 gene amplification may be detected by fluorescence in situ hybridization (FISH).[5,6] Historically, HER2+ and triple-negative BC subtypes carried the poorest prognosis, with the highest recurrence and mortality rates.[7] HER2+ BC also has a higher propensity for intracranial metastasis, which is associated with a worse prognosis.[8] The discovery that HER2 was a major oncogenic driver and treatment target led to transformative therapeutic advances over the last 25 years.[7] Specifically, the HER2-targeted monoclonal antibody trastuzumab, combined with chemotherapy, improved disease-free survival (DFS) and overall survival (OS) in adjuvant and metastatic settings,[9] with a 50% reduction in recurrence and 30% improvement in survival.[3] Since then, other HER2-directed therapies have added to this benefit.[4] Currently, most patients diagnosed with stage I to III HER2+ BC are cured. Of patients who initially present with de novo MBC, 40% to 50% of cases are HER2+,[7] which reflects the high cure rates. However, despite remarkable advances, intrinsic and acquired resistance to HER2-directed therapies remains a vexing challenge, and prevention and treatment options for patients with HER2+ breast cancer brain metastases (BCBM) remain suboptimal.[10] Recently, a new category of patients with "HER2-low" BC were identified (~45%-55% of all BCs, that is, HER2 IHC 1+ or 2+ in the absence of HER2 gene amplification by FISH);[11] this subtype can respond well to HER2-targeted antibody-drug conjugates (ADCs).[12] Reviews detailing management options for HER2-low MBC are available elsewhere.[13,14]

Current Standard of Care

There are 8 FDA-approved HER2+ targeted treatments for HER2+ MBC: monoclonal antibodies (mAb) (trastuzumab

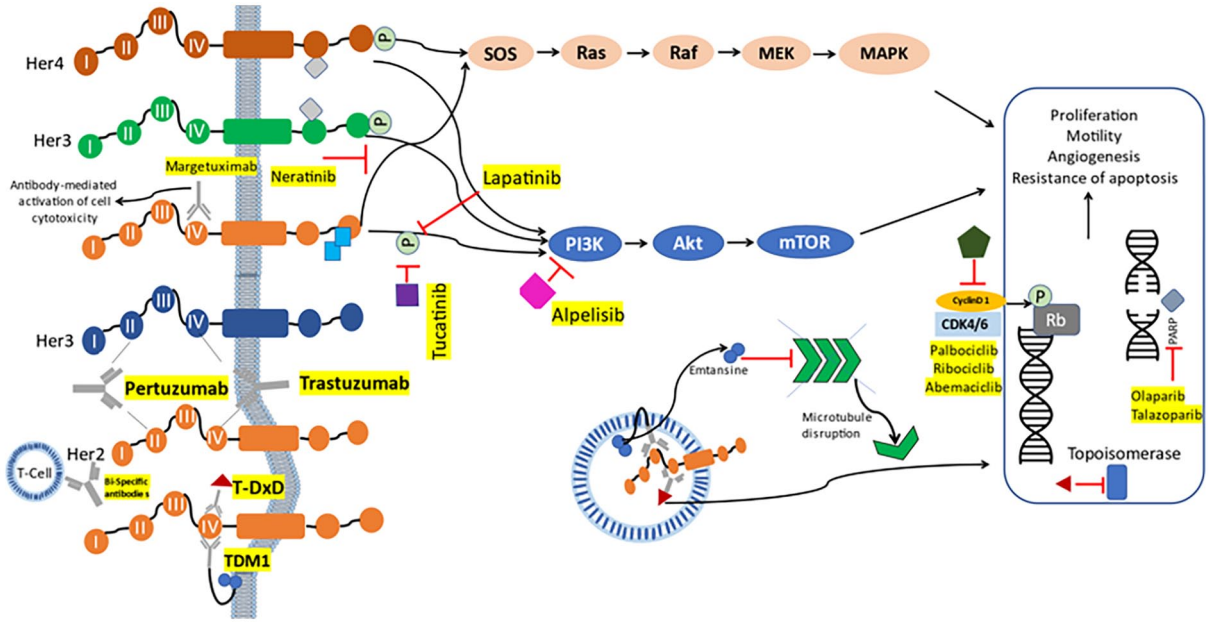

Figure 1. HER2 signaling pathways. Mechanism of action of standard and novel HER2-directed therapies. Approved HER2-directed therapies include *trastuzumab*, which binds to the juxtamembrane extracellular subdomain IV of human epidermal growth factor receptor 2 (HER2) resulting in the inhibition of HER2 signaling; *pertuzumab*, which binds to the HER2 subdomain inhibiting homodimerization and heterodimerization of HER2 and HER3; *ado-trastuzumab emtansine, T-DM1*, which is an antibody-drug conjugate (ADC) that includes trastuzumab linked to emtansine, a microtubule inhibitor which is released after ADC phagocytosis from intracellular lysosomes; *trastuzumab deruxtecan, T-DXd*, which is another ADC comprised of trastuzumab and deruxtecan and is considered a potent topoisomerase I inhibitor; *margetuximab*, a monoclonal antibody (mAb) ADC that combines trastuzumab with an altered FC-γ domain causing T-cell activation and antibody-mediated cell cytotoxicity; *lapatinib*, a reversible tyrosine kinase inhibitor (TKI) of HER1 and HER2 that inhibits further downstream pathway signaling (AKT, PI3K, RAS/RAF/MEK/MAPK); *neratinib*, which is a TKI that inhibits HER1, HER2, and HER4; and *tucatinib*, which is a HER2-specific TKI. Other targeted therapies shown include the *PI3K inhibitor* alpelisib; and cyclin-dependent kinase 4 (CDK4) and CDK6 inhibitors (*CDK4/6i*) (palbociclib, ribociclib, and abemaciclib), which have or are currently being studied in clinical trials in combination with HER2-targeted agents . Olaparib and talazoparib (*PARP inhibitors*) ultimately result in DNA breaks and impair DNA repair pathways. *Bispecific antibodies* are currently being studied in clinical trials, linking various domains of HER2 to specific ligands on T cells, resulting in T-cell-mediated death.

[Herceptin], pertuzumab [Perjeta], and margetuximab [Margenza]); antibody-drug conjugates (ADCs) (ado-trastuzumab emtansine [T-DM1], fam-trastuzumab deruxtecan [T-Dxd]), and tyrosine kinase inhibitors (tucatinib [Tuksya], lapatinib [Tykerb], neratinib [Nerlynx] and pyrotinib [approved for use in China, but not in the United States]). Table 1 shows approved therapies for HER2+ MBC, including toxicity and efficacy data from seminal trials.

HER2-Targeted Therapies

Monoclonal antibodies

In 1998, trastuzumab was FDA-approved in combination with paclitaxel for treatment of HER2+ MBC. Notable side effects of trastuzumab included cardiomyopathy, pulmonary toxicity, and infusion reactions.[3,28] Pertuzumab was FDA-approved in 2012 in combination with trastuzumab and docetaxel for the 1L treatment of HER2+ MBC based on the phase III CLEOPATRA trial.[29] For patients with HER2+ MBC treated with docetaxel, trastuzumab + pertuzumab (THP) versus docetaxel, trastuzumab + placebo (TH) in the 1L metastatic setting, 8-year OS rates were 37% in the pertuzumab arm versus 23% in the placebo arm, conferring an approximately 16-month OS advantage favoring THP.[15,30] Notable adverse effects included diarrhea, rash, and cardiomyopathy. Several trastuzumab (±pertuzumab) biosimilars have been approved for use in HER2+ BC.[31] Benefits include the option of subcutaneous administration in some cases, which is quicker and convenient, as well as reduced costs for patients and oncology infusion centers.[32] However, widespread adoption has been slow, due to concerns regarding efficacy and insurance issues.[33,34]

Margetuximab is a novel Fc-engineered HER2-targeted mAb that triggers innate and adaptive immunity.[35] The Fc fragment targets the same epitope as trastuzumab and was manufactured to increase affinity for activating CD16A (FcγRIIIA) and decrease binding to inhibitory CD32B (FcγRIIB).[16,36] In the SOPHIA trial, patients with HER2+ MBC who had received ⩾2 lines of HER2-targeted therapies were randomized 1:1 to investigator's choice of chemotherapy + trastuzumab or chemotherapy + margetuximab. The median OS (mOS) was 21.6 months with margetuximab versus 21.9 months with trastuzumab ($P = .620$). A preplanned, exploratory analysis of CD16A genotyping noted a possible OS improvement for margetuximab in CD16A-158FF patients versus trastuzumab (mOS, 23.6 vs 19.2 months) and a possible OS improvement for trastuzumab in CD16A-158VV patients versus margetuximab (mOS, 31.1 vs 22.0 months). Margetuximab and trastuzumab had comparable safety profiles. Final overall OS analysis was not significantly increased in the margetuximab arm.[16,17]

Table 1. Approved treatments for HER2+ MBC.

AGENT	MECHANISM OF ACTION	LANDMARK TRIAL (S) THAT LED TO REGULATORY APPROVAL IN HER2+ MBC	SYSTEMIC TREATMENT REGIMENS	TRIAL RESULTS	TREATMENT SETTING	NOTABLE SIDE EFFECTS	YEAR OF FDA APPROVAL FOR HER2+ MBC	FDA INDICATION FOR USE
Monoclonal antibodies (mAbs)								
Trastuzumab (Herceptin)	Humanized monoclonal ab against HER2 ectodomain Antibody-dependent cell-mediated cytotoxicity (ADCC)	Slamon et al[3] Phase III	Chemotherapy alone vs chemotherapy + trastuzumab No prior anthracycline: pts received AC or EC ± trastuzumab Prior anthracycline: paclitaxel ± trastuzumab	Median TTP, 7.4 (trastuzumab group) vs 4.6 mos. (chemo alone group) [$P < .001$] OR, 50% trastuzumab group vs 32% chemo alone group, [$P < .001$] OS, 45% trastuzumab group vs 29% chemo along group [$P < .001$] (Slamon et al[3])	HER2+ MBC (1L)	NYHA III or IV: 16% in anthracycline, cyclophosphamide + trastuzumab group, 3% in anthracycline + cyclophosphamide group, and 2% in paclitaxel + trastuzumab group, 1% with paclitaxel alone	1998	(1) In combination with paclitaxel for 1L Tx of HER2+ MBC (2) as a single agent for HER2+ MBC who received ⩾1 chemotherapy regimen(s)for HER2+ MBC
Pertuzumab (Perjeta)	Monoclonal ab that binds domain II of HER2. Inhibits HER2/HER3 dimerization receptors	CLEOPATRA[15] (NCT00567190) Phase III	pertuzumab, trastuzumab + docetaxel compared with placebo, trastuzumab + docetaxel	mPFS: 18.7 mos. in pertuzumab group [HR, 0.69, 95% CI, 0·59-0·81], 12.4 mos. in the placebo group [95% CI, 10-14]. OS: 57.1 mos. in pertuzumab group, 40.8 mos. in placebo group [HR, 0.69, 95% CI, 0.58-0.82], 8-year OS rates 37% in pertuzumab group, 23% in the placebo group (Swain et al[15])	HER2+ MBC (1L)	Most common grade 3/4 AEs: neutropenia 49% in the pertuzumab group (11% febrile neutropenia), 46% in the placebo group (5% febrile neutropenia)	2012	In combination with trastuzumab and docetaxel for patients with HER2+ MBC who haven't received prior HER2-targeted therapy for MBC
Margetuximab (Margenza)	Novel Fc-engineered HER2-targeted IgG ab that stimulates innate and adaptive immunity, increases affinity to bind CD16A and decreases affinity to bind CD32B	SOPHIA (NCT02492711) Phase III	margetuximab plus chemotherapy vs trastuzumab plus chemotherapy	OS 21.6 mos. in the margetuximab group vs 19.8 mos. in the trastuzumab group[$P = .33$] 29% RRR favoring margetuximab [$P < .001$] median, 5.7 vs 4.4 mos. ORR 25% vs 14% [$P < .001$] (Rugo et al[16]) Update 2023: Final overall OS analysis not increased in margetuximab arm, 21.6 mos. with margetuximab vs 21.9 months with trastuzumab ($P = .620$) (Rugo et al[17])	HER2+ MBC after progression on ⩾2 prior HER2-directed therapies (3L+)	Most common grade 3+ AEs: neutropenia (19.7% in margetuximab group, 12.4% in trastuzumab group); anemia (4.9% in margetuximab group, 6.4% in trastuzumab group) All grade, IRRs margetuximab (13.3%) vs trastuzumab (3.4%), grade III LVSD: 1.1% margetuximab group, and 0.4% trastuzumab group	2020	In combination with chemotherapy, for patients with HER2+ MBC who have received ⩾2 prior HER2-targeted regimens, ⩾1 for metastatic disease

(Continued)

Table 1. (Continued)

AGENT	MECHANISM OF ACTION	LANDMARK TRIAL (S) THAT LED TO REGULATORY APPROVAL IN HER2+ MBC	SYSTEMIC TREATMENT REGIMENS	TRIAL RESULTS	TREATMENT SETTING	NOTABLE SIDE EFFECTS	YEAR OF FDA APPROVAL FOR HER2+ MBC	FDA INDICATION FOR USE
Tyrosine kinase inhibitors (TKIs)								
Lapatinib (Tykerb)	Selective, reversible ATP competitive TKI of HER2 and EGFR	(NCT00078572) Phase III	Lapatinib (L) + Capecitabine (C) vs C monotherapy	Median 8.4 mos. with L + C vs 4.4 mos. with C monotherapy . [$P < .001$] (Geyer et al[18])	HER2+ MBC after progression on trastuzumab (2L)	Grade III diarrhea 12% in L + C group, 11% in C group, grade 4 diarrhea 1% in L + C group; 0% in C group, grade 3+HFS 7% in L + C group, 11% in C group	2007	In combination with capecitabine for treatment of HER2+ MBC post prior anthracycline, taxane and trastuzumab or in combination with letrozole for treatment of HER2+ MBC when endocrine therapy utilized
Neratinib (Nerlynx)	Potent, low molecular weight, irreversible pan-HER TKI which binds covalently to the intracellular TKI and inhibits autophosphorylation with downstream signaling	NALA (NCT01808573) Phase III	Neratinib (N) + capecitabine (C) vs L + C	PFS was improved with N + C by ~2 mos. compared to L + C; HR, 0.76 [$P = .0059$] OS was improved by 1.7 mos. with N + C vs L + C, HR, 0.88 [$P = .2098$]—not statistically significant ORRs 32.8% for N + C vs 26.7% for L + C [$P = .1201$] median DoR was 8.5 with N + C versus 5.6 mos. [$P = .0004$] Fewer interventions for CNS disease with N + C vs L + C (CI, 22.8% vs 29.2%) [$P = .043$] (Saura et al[19])	HER2+ MBC, status post ⩾2 lines of HER2+ directed treatments (3L+)	Grade 3/4 diarrhea in 24.4% of patients in N + C group vs 12.5% in L + C group Most common grade 3/4 AEs: PPES (9.6% in N + C and 11.6% in L + C arm) and 4.6% hypokalemia in N + C and 6.4% in L + C arm)	2020	In combination with capecitabine for the Tx of advanced or HER2+ MBC who have received ⩾2 prior anti-HER2-targeted therapies in the metastatic setting

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Table 1. (Continued)

AGENT	MECHANISM OF ACTION	LANDMARK TRIAL (S) THAT LED TO REGULATORY APPROVAL IN HER2+ MBC	SYSTEMIC TREATMENT REGIMENS	TRIAL RESULTS	TREATMENT SETTING	NOTABLE SIDE EFFECTS	YEAR OF FDA APPROVAL FOR HER2+ MBC	FDA INDICATION FOR USE
Tucatinib (Tukysa)	Potent HER2-selective TKI	HER2Climb (NCT02614794) Phase III	Tucatinib + capecitabine + trastuzumab vs placebo + capecitabine + trastuzumab	mOS 21.9 mos. in the tucatinib group (95% CI, 18.3-31.0) vs 17.4 mos. in the placebo group (95% CI, 13.6-19.9) Risk of death 34% lower in the tucatinib group (HR, 0.66) [$P = .005$) HER2+ BCBM: PFS 1 year was 24.9% vs 0% in placebo arm; PFS 7.6 mos. vs 5.4 mos. The risk of POD or death was 52% lower in the tucatinib group (HR, 0.48) [$P < .001$] (Murthy et al[20]) Separate analysis of BCBM The risk of intracranial progression or death was reduced by 68% in the tucatinib arm [HR, 0.32; 95% CI, 0.22-0.48; $P < .0001$)] Median CNS-PFS was 9.9 mos. in the tucatinib arm (95% CI, 8.0-13.9 mos.) vs 4.2 mos. in placebo arm (95% CI, 3.6-5.7 mos.) (Lin et al[21]) Updated analysis: mOS 9.1 mos. longer in the tucatinib arm (21.6 months; 95% CI, 18.1-28.5) vs the placebo arm (12.5 months; 95% CI, 11.2-16.9). (Lin et al[22])	HER2+ MBC, ⩾2 previous HER2-directed MBC therapies, including selected patients with BCBM. Approximately 50% of pts had BCBM at enrollment; ~40% of these had untreated or previously Tx BCBM	Grade 3+ AEs: diarrhea 12.9% in tucatinib group vs 8.6% in the placebo group, PPES 13.1% in tucatinib group vs 9.1% in placebo group	2020	In combination with trastuzumab and capecitabine for patients with HER2+ MBC, ±BCBM, who have received ⩾1 prior HER2+-directed therapies in the metastatic setting
Pyrotinib	Irreversible TKI that targets HER1, HER2, and HER4	PHOEBE (NCT03080805) Phase III (conducted in China) PHILA[23] (NCT 03863223) Phase III (conducted in China)	Pyrotinib (P) + capecitabine (C) vs lapatinib (L) + capecitabine(C) Pyrotinib (P), trastuzumab (H) and docetaxel (T) vs placebo, trastuzumab (H) and docetaxel (T)	PFS 12.5 mos. in P + C arm vs 6.8 mos. in L + C arm (HR, 0.39) [$P < .0001$] (Xu et al[24]) PFS 24.3 mos. in P + H + T arm (95% CI, 19.1-33 mos.) vs 10.4 mos. (9.3-12.3 mos.) in placebo + H + T arm [$P < .001$] (Ma et al[23])	In patients with prior taxane and trastuzumab exposure In patients with untreated HER2+ MBC	Grade 3 AE: diarrhea 31% in P group vs 8% in L group HFS 16% in the P group vs 15% in the L group Grade 3 AE: Diarrhea 46% in P + H + T vs 3% in placebo + H + T arm Grade 3 neutropenia 63% in P + H + T vs 65% in placebo + H + T arm	Not FDA approved	N/A Approved as 2L treatment for HER2+ MBC in China

(Continued)

Table 1. (Continued)

AGENT	MECHANISM OF ACTION	LANDMARK TRIAL (S) THAT LED TO REGULATORY APPROVAL IN HER2+ MBC	SYSTEMIC TREATMENT REGIMENS	TRIAL RESULTS	TREATMENT SETTING	NOTABLE SIDE EFFECTS	YEAR OF FDA APPROVAL FOR HER2+ MBC	FDA INDICATION FOR USE
Antibody-drug conjugates (ADCs)								
Ado-trastuzumab emtansine T-DM1 (Kadcyla)	Conjugate of trastuzumab and antimicrotubule compound DM1	EMILIA trial (NCT00829166) Phase III	T-DM1 vs lapatinib (L) + capecitabine (C)	mPFS of 9.6 mos. in T-DM1 arm vs 6.4 mos. with L + C [$P < .0001$] ORR 43.6% vs 30.8% [$P < .001$] (Verma et al[25])	HER2+ advanced breast cancer previously treated with trastuzumab and a taxane	Diarrhea (20.7%) and PPES (16.4%) were the most common grade 3 or 4 events in the L + C group compared with 1.6% and 0%, respectively, in the T-DM1 group Most common grade 3/4 AE with T-DM1 were TCP (12.9%) and elevated transaminases 4.3%/2.9% vs TCP 0.2% in L + C group and elevated transaminases 1.4%/0.8% in the L + C group	2013	As a single agent for treatment of pts with HER2+ MBC who previously received trastuzumab and a taxane
Trastuzumab -Deruxtecan (T-DXd) (Enhertu)	Binds to HER2 on tumor cells, undergoing internalization and intracellular linker cleavage via lysosomal enzymes. Then membrane-permeable DNA topoisomerase I inhibitor enters the nucleus. After cleavage and release, DXd causes targeted DNA damage and apoptosis in cancer cells, due to the ability to cross cell membranes.	DESTINY-Breast01 (NCT03248492) Phase II DESTINY Breast-03 (NCT03529110) Phase III	*DB01: -DXd* in adults with HER2+ MBC who had received prior T-DM1 *DB03:* Trastuzumab Emtansine (T-DM1) vs Trastuzumab Deruxtecan (T-DXd) in patients previously Tx with taxane and trastuzumab ± BCBM	*DB01*: Median DoR 14.8 mos. (95% CI, 13.8-16.9) in T-DXd mPFS was 16.4 mos. in T-DXd (CI not reached) overall RR 60.9% in T-DXd (Modi et al[26]) DB03: mPFS 28·8 mos. (95% CI, 22.4-37.9) with T-DXd vs 6·8 mos. (5.6-8.2) with T-DM1 (HR, 0.33 [95% CI, 0.26-0.43]; nominal P < .0001). mOS not reached (95% CI, 40.5 months-not estimable), with 72 (28%) OS events in T-DXd group and not reached (34.0 mos.-not estimable), with 97 (37%) OS events, in T-DM1 group (HR, 0.64 [95% CI, 0.47-0.87]; P = .0037). (Cortés et al[27])	HER2+ MBC, previously treated with trastuzumab and taxane (both DB01 and DB03)	*DB01*: Grade 3+, neutropenia 20.7% anemia 8.7%, and nausea 7.6% ILD in 13.6% (grade 1 or 2, 10.9%; grade 3 or 4, 0.5%; and grade 5, 2.2%) in T-DXd *DB03:* Drug-related ILD or pneumonitis (G1-3 only) in 10.5% of T-DXd group vs 1.9% in T-DM1 Grade 3 or 4 AEs in T-DXd group were neutropenia (19.1%), TCP 7.0%), leukopenia (6.6%), and nausea (6.6%) vs 3.1%, 24.9%, 0.4%, and 0.4%, respectively, in T-DM1 group.	2019 (3L)- DB01 2022 (2L) DB03	- HER2+ MBC pts who have received ⩾ 2 HER2-directed regimens in the 3L metastatic setting - HER2+ MBC pts who have received ⩾ 1 HER2-targeted regimens in the 2L metastatic setting

Abbreviations: ab, antibody; AC, doxorubicin + cyclophosphamide; ADCC, antibody-dependent cell-mediated cytotoxicity; AE, adverse events; AKI, acute kidney injury; BCBM, breast cancer brain metastases; BM, brain metastasis; C, capecitabine; CI, confidence interval; DP, disease progression; DB01, Destiny-Breast01; DB03, Destiny-Breast03; DoR, duration of response; EBC, early breast cancer; EC, epirubicin + cyclophosphamide; Erβ, estrogen receptor beta; FDA, Food and Drug Administration; HFS, hand foot syndrome; HR, hazard ratio; ICP, intracranial pressure; IRR, infusion-related reaction; L, lapatinib; LVSD, left ventricular systolic dysfunction; MBC, metastatic breast cancer; mPFS, median progression-free survival; mos., months; mOS, median overall survival; N, neratinib; OR, objective response; ORR, overall response rate; OS, overall survival; P, pyrotinib; PFS, progression-free survival; PE, pulmonary embolism; POD, progression of disease; PPES, palmar-plantar erythrodysesthesia syndrome; pts, patients; RRR, relative risk reduction; SAH, subarachnoid hemorrhage; TCP, thrombocytopenia; TKI, tyrosine kinase inhibitors; TTP, time to progression; 1L, first line; 2L, second line; 3L, third line.

The most common AEs in the margetuximab arm were fatigue, nausea, vomiting, diarrhea, and LV dysfunction.[37] Going forward, margetuximab studies in HER2+ BC with different CD16A allelic variants could be conducted.

Tyrosine kinase inhibitors

Tyrosine kinase inhibitors (lapatinib, neratinib, tucatinib, and pyrotinib) are an orally administered treatment option for HER2+ MBC. They differ by HER protein specificity, molecular weight, binding reversibility, and side-effect profiles.[38] All are FDA-approved in HER2+ MBC, except pyrotinib. GI, cutaneous, and hepatotoxicities are commonly encountered. In 2007, lapatinib, combined with the 5-fluorouracil prodrug capecitabine, was the second HER2-targeted agent FDA-approved for HER2+ MBC. A phase III trial showed that for patients with HER2+ MBC previously treated with taxane and trastuzumab, lapatinib + capecitabine improved progression-free survival (PFS) versus capecitabine alone (8.4 vs 4.4 months; $P < .001$).[39] This regimen was the preferred 2L option until superseded by T-DM1 in 2013, based on the EMILIA trial.[25]

In 2020, neratinib + capecitabine was FDA-approved based on the NALA trial (n = 621), wherein patients with HER2+ MBC post ⩾2 prior lines of HER2-directed therapy for MBC were randomized 1:1 to neratinib + capecitabine or lapatinib + capecitabine.[19] Approximately one third of participants had received prior T-DM1, trastuzumab and pertuzumab. A 2.2-month PFS gain ($P = .0003$) and a 1.8-month OS gain ($P = .208$) were noted in the neratinib arm, which led to FDA approval of neratinib + capecitabine in 2020. Regarding CNS outcomes, there was delayed time to intervention for and reduced cumulative incidence of BCBM in the neratinib arm. Regarding toxicities, 24% of patients in the neratinib arm had grade 3 or 4 diarrhea; however, treatment discontinuations due to treatment-related AE were comparable.[19] The CONTROL trial subsequently showed improved neratinib tolerability with dose escalation over the initial 2 weeks of therapy.[40]

Tucatinib + trastuzumab + capecitabine was FDA-approved for 3L treatment of HER2+ MBC in 2020[21] based on results from the HER2CLIMB study (NCT02614794),[20] wherein 612 patients were randomized 2:1 to capecitabine, trastuzumab + tucatinib versus capecitabine, trastuzumab + placebo. All participants had received prior T-DM1, pertuzumab, and trastuzumab. A median of 3 prior lines of treatment had been administered in the metastatic setting. Nearly half of the enrollees had BCBM and ~40% had untreated or previously treated and progressing BCBM, which was unique, as stable BCBM were usually required for study enrollment. Median PFS (mPFS) was 7.6 versus 4.9 months for the tucatinib versus placebo arm ($P < .00001$).[41] Median overall survival (mOS) was 24.7 versus 19.2 months in the tucatinib versus placebo arm ($P = .004$), respectively. Tucatinib-based therapy was well tolerated with low discontinuation rates. In BCBM, addition of tucatinib to trastuzumab + capecitabine improved intracranial objective response rate (RR) (47.3% vs 20.0%, $P = .03$), reduced risk of intracranial progression or death by 68%, and reduced risk of death by 42%, with prolongation of OS by ⩾6 months.[21] An updated analysis showed mOS was 9.1 months longer in the tucatinib arm (21.6 months; 95% CI, 18.1-28.5) versus the placebo arm (12.5 months; 95% CI, 11.2-16.9).[22] The risk of developing new BCBM as a site of first progression or death was reduced by 45.1% in the tucatinib arm versus the placebo arm (hazard ratio [HR], 0.55; 95% CI, 0.36-0.85).[22] Currently, tucatinib, capecitabine + trastuzumab is a 2L or 3L treatment for HER2+ MBC.

HERCLIMB-02 (NCT03975647) was a double-blind phase III trial of tucatinib + T-DM1 which included patients with HER2+ MBC previously treated with trastuzumab and a taxane. A significant improvement in mPFS was noted in the T-DM1 arm (9.5 months) versus 7.4 months in the placebo arm ($P = .0163$), with a decreased risk of progression or death by 24.1% in the tucatinib arm.[42] Furthermore, mPFS in patients with BCBM was 7.8 months (tucatinib arm) versus 5.7 months (placebo arm) (HR, 0.64). Although a higher rate of G3 hepatic AEs was seen in the tucatinib arm (AST/ALT elevations; 28.6% vs 7.3%), AEs were typically short-lived and manageable. If T-DM1 + tucatinib is FDA-approved, incorporation into treatment algorithms for HER2+ MBC as a joint third- or fourth-line treatment option is likely. Limitations include immature OS data at writing and the inability to compare the HER2CLIMB-02 regimen to T-DXd or the HER2CLIMB regimen. Importantly, HERCLIMB-02 is the second randomized trial showing that tucatinib-based therapy delays progression in HER2+ BCBM.

In 2020, pyrotinib + capecitabine was approved for 2L treatment of HER2+ MBC in China, based on results from PHOEBE which enrolled patients with HER2+ MBC who had received ⩽2 lines of chemotherapy for metastatic disease, including trastuzumab and taxanes. Patients were randomized 1:1 to pyrotinib or lapatinib + capecitabine. Pyrotinib + capecitabine improved PFS versus lapatinib + capecitabine (12.5 vs 5.6 months; $P < .0001$). mOS was not reached in the pyrotinib group and was 26.9 months (22.4-not reached) in the lapatinib group.[24] Pyrotinib-based therapy is an option in regions of China that do not have access to ADCs. It is unclear whether pyrotinib will be used internationally in the future.

Antibody-drug conjugates

Antibody-drug conjugates combine an antigen-specific antibody backbone with a potent cytotoxic payload, resulting in an improved therapeutic index. T-DM1 combines trastuzumab with the maytansinoid, DM1 (a potent microtubule-disrupting agent), joined by a stable linker.[25,43] T-DXd has a higher drug: antibody ratio (~8:1) versus T-DM1 (~3.5:1) and inhibits

topoisomerase I versus microtubule inhibition.[44] The high membrane permeability of DXd facilitates local bystander effects, inducing malignant cell death in the tumor microenvironment.[44] Side effects of HER2-targeted ADCs include cytopenias, nausea, and interstitial lung disease (ILD). In 2013, T-DM1, the prototype ADC, was FDA-approved for 2L treatment of HER2+ MBC based on EMILIA (NCT00829166) which showed that T-DM1 increased PFS in HER2+ MBC post trastuzumab and a taxane, versus lapatinib + capecitabine (9.6 vs 6.4 months, respectively; $P < .001$).[25] mOS was also superior in the T-DM1 arm (30.9 vs 25.1 months, [$P < .001$]). T-DM1 was the standard 2L option until 2021 when superseded by T-DXd, based on striking results from the phase III DESTINY Breast03 trial (DB03). DB03 randomized patients with HER2+ MBC +/- BCBM, previously treated with taxane and trastuzumab, to T-DM1 versus T-DXd.[27] Updated results showed that PFS was 28.8 months with T-DXd and 6.8 months with T-DM1 (HR, 0·33; $P < .0001$); mOS not reached in either arm.[45] The incidence of ⩾grade 3 AEs was similar. Drug-related ILD occurred in 15% patients on T-DXd versus in 3% on T-DM1, with no grade 4 or 5 events. Following accelerated FDA approval in the 3L HER2+ MBC setting,[46] T-DXd was subsequently approved in the 2L in 2022. Results from DESTINY-Breast09 (NCT04784715) will determine whether T-DXd will replace THP as 1L treatment for HER2+ MBC.

Triple-positive MBC

Targeting both ER and HER2 is relevant in patients with HR+ HER2+ MBC, as there is signaling overlap between the pathways and dual inhibition is more effective.[47] Combination of an aromatase inhibitor + HER2-targeted therapy (ie, trastuzumab + pertuzumab) as evaluated in the PERTAIN trial is an option for older patients who are not chemotherapy candidates.[48]

Evolving treatment and sequencing considerations

The treatment landscape for HER2+ MBC is crowded. Treatment decisions are influenced by patient comorbidities, potential toxicities, and activity against BCBM, PFS, and OS data. Evaluation of novel compounds and regimens is underway and will further impact treatment sequencing in the future. Currently, standard 1L therapy remains THP based on the 16-month OS advantage noted in CLEOPATRA.[15] For patients relapsing ⩽6 months after completion of adjuvant therapy, and for those relapsing ⩽12 months from completion of pertuzumab-based adjuvant treatment, T-DXd is the preferred 1L option. For patients relapsing 6 to 12 months after non-pertuzumab-based adjuvant treatment, 1L THP is recommended.[49] T-DXd is standard 2L therapy; however, tucatinib, capecitabine + trastuzumab is an acceptable 2L option for patients unable to tolerate T-DXd or for isolated CNS progression. Apart from tucatinib, trastuzumab + capecitabine, other regimens used in the 3L and beyond include (1) neratinib + capecitabine, (2) margetuximab + chemotherapy, (3) T-DM1 (if not previously administered), (4) lapatinib + trastuzumab, (5) chemotherapy + trastuzumab, and (6) endocrine therapy (ET) + trastuzumab (HR+ disease). Other questions relate to activity of (1) neratinib after a tucatinib-based regimen, and (2) T-DM1 after progression on T-DXd. As T-DM1 and T-DXd have different chemotherapy moieties, response is theoretically possible. Ongoing trials of FDA-approved targeted therapies in HER2+ MBC are shown in Table 2.

The current treatment paradigm for HER2+ MBC is shown in Figure 2. In the future, predictive biomarkers may identify which patients can discontinue therapy safely. Other patients may exhibit intrinsic or acquired resistance to HP based therapy in the 1L and could benefit from therapy change or escalation. For example, mutation activation within the PI3K pathway with ERBB3 mutation, PIK3CA mutation, and PTEN loss alters HER2-targeted efficacy. MAPK mutations ultimately can lead to variations in pathway dependence (eg, a PI3K/AKT to ERK/MEK switch) causing HER2 resistance and MEK inhibitor sensitivity.[50]

De-escalation strategies

Personalization of therapy as it relates to de-escalation versus escalation is an important principle. Some patients are exceptional responders to 1L HER2-targeted therapy and remain in remission on maintenance trastuzumab ± pertuzumab for years after induction therapy. An important question is the optimal selection strategy and timeline for discontinuation of maintenance therapy in a subset of patients with HER2+ MBC.

In HER2+ EBC, pathologic complete response to preoperative systemic therapy is an established tool to guide therapy de-escalation or escalation. In HER2+ MBC, a subset of patients with HER2+ MBC on 1L maintenance therapy (trastuzumab + pertuzumab) have extended PFS and OS (8-year OS 37% in CLEOPATRA).[15] Therefore, some patients may be cured but nevertheless continue HER2-directed therapy, which, although well tolerated, could be associated with unnecessary expense and patient inconvenience. As minimal residual disease assays are correlated with response in HER2+ exceptional responders,[51] the hypothesis of STOP-HER2 (NCT05721248) is that selected patients with HER2+ MBC can safely stop HER2-directed treatment. STOP-HER2 is enrolling patients who are progression free after ⩾3 years on 1L HER2-targeted therapy. Participants stop therapy with close follow-up and extensive biomarker assessment. A parallel, observational cohort enrolls patients who prefer to continue therapy. Primary goals are to evaluate 1-year PFS in patients with HER2+ MBC and exceptional response to HER2-targeted therapy who either continue or stop the same. SAPPHO is a phase II study in development which will test efficacy of a sequential

Table 2. Selected trials of FDA-approved HER2-directed therapies in HER2+ MBC currently recruiting participants.

DRUG CLASS	DRUG NAME	NCT	TRIAL PHASE	TRIAL NAME	TARGET POPULATION	OTHER AGENTS	PRIMARY OUTCOME MEASURE	START DATE	ESTIMATED PRIMARY COMPLETION DATE
ADC	T-DXd	NCT04784715	III	Trastuzumab Deruxtecan (T-DXd) With or Without Pertuzumab Versus Taxane, Trastuzumab and Pertuzumab in HER2-positive Metastatic Breast Cancer **(DESTINY-Breast09)**	HER2+ MBC 1L	pertuzumab, trastuzumab	PFS	4/26/2021	3/28/25
	T-DXd	NCT05458401	n/a	European Real-world Experience Of Previously Treated Advanced/Metastatic HER2-positive Breast Cancer Patients Accessing Trastuzumab Deruxtecan **(EUROPA T-DXd)**	HER2+ MBC on T-DXd	N/A	Real-world time-to-treatment discontinuation in participants treated with T-Dxd	11/11/22	9/30/23
TKI	Tucatinib	NCT05230810	I/II	Clinical Trial of Alpelisb and Tucatinib in Patients With PIK3CA-Mutant HER2+ Metastatic Breast Cancer	PIK3CA-mutated HER2+ MBC (3L+)	Alpelisib ± Fulvestrant	Ib- MTD II- PFS	8/25/22	6/30/23
	Tucatinib	NCT05748834	II	Study of Tucatinib and Doxil in Participants With Human Epidermal Growth Factor Receptor 2 Positive (HER2+) Metastatic Breast Cancer	HER2+ MBC (2L+)	Doxil	ORR	06/2023	07/2026
	Tucatinib	NCT05583110	II	Efficacy and Safety of the Combination of Trastuzumab Plus TUCAtinib Plus viNorelbine in Patients With HER2-positive Nonresectable Locally Advanced or Metastatic Breast Cancer (**TrasTUCAN**)	HER2+ MBC, ⩾2 prior Tx For EBC and or MBC	Vinorelbine trastuzumab	ORR	3/8/23	8/2026
	Tucatinib	NCT03975647	III	A Study of Tucatinib vs Placebo in Combination With Ado-trastuzumab Emtansine (T-DM1) for Patients With Advanced or Metastatic HER2+ Breast Cancer **(HER2CLIMB-02)**	HER2+MBC, Progression on taxane and trastuzumab	T-DM1	PFS	10/2/19	4/30/24
	Tucatinib	NCT04539938	II	A Study of Tucatinib Plus Trastuzumab Deruxtecan in HER2+ Breast Cancer **(HER2CLIMB-04)**	HER2 + MBC 2L	T-Dxd	cORR	12/1/20	07/31/23
	Tucatinib	NCT05132582	III	A Study of Tucatinib or Placebo With Trastuzumab and Pertuzumab for Metastatic HER2+ Breast Cancer **(HER2CLIMB-05)**	HER2+ MBC 1L	pertuzumab, trastuzumab	PFS	3/7/22	10/31/24

(Continued)

Table 2. (Continued)

DRUG CLASS	DRUG NAME	NCT	TRIAL PHASE	TRIAL NAME	TARGET POPULATION	OTHER AGENTS	PRIMARY OUTCOME MEASURE	START DATE	ESTIMATED PRIMARY COMPLETION DATE
	Tucatinib	NCT05892068	II	A Study of Tucatinib Given Before Surgery to People With HER2+ Cancers That Have Spread to the Brain	HER2+ AST ± LMD	N/A	Cmax Tucatinib 3 days after Tx by measurement of intrametastasis levels	05/09/23	05/09/28
	Tucatinib	NCT05041842	II	Treatment With Tucatinib in Patients With an Isolated Brain Progression of a Metastatic Breast Cancer (InTTercePT)	HER2+ MBC, Isolated CNS progression	pertuzumab, trastuzumab ± ET	PFS (6 months)	12/17/21	12/30/24
	Tucatinib	NCT05319873	I/II	Ribociclib, Tucatinib, and Trastuzumab for the Treatment of HER2 Positive Breast Cancer	Phase I: HER2+ MBC (2L+) Phase 2: EBC	ribociclib, trastuzumab	Phase Ib: MTD Phase 2: pCR	4/7/22	4/7/24
	Tucatinib	NCT05458674	II	A Study of the Safety, Tolerability and Antitumor Activity of Tucatinib in Combination With Eribulin and Trastuzumab in Patients With Pretreated Unresectable Locally Advanced or Metastatic HER2+ Breast Cancer	HER2+ MBC, Progression on taxane and trastuzumab (prior tucatinib allowed)	eribulin, trastuzumab	Safety and tolerability	11/17/22	11/26/23
	Tucatinib	NCT05323955	II	Secondary Brain Metastases Prevention After Isolated Intracranial Progression on Trastuzumab/Pertuzumab or T-DM1 in Patients With aDvanced Human Epidermal Growth Factor Receptor 2+ brEast Cancer With the Addition of Tucatinib (BRIDGET)	HER2+ MBC BM (on 1L HP or 2L T-DM1 or isolated BM)	pertuzumab, trastuzumab; T-DM1	PFS	4/12/22	6/22/23
TKI	Neratinib	NCT04517838	Observational (correlative)	Immune Response to Anti-HER2 Therapies in Patients With HER2-Positive Stage I-IV Breast Cancer	HER2+ BC, stage I-IV	All other HER2-directed therapies	Correlation between clinical response and (1) HER2-specific T-cell response and (2) antibody response	8/18/20	2/6/23

Abbreviations: ADC, antibody-drug conjugate; AST, advanced solid tumors; BM, brain metastases; Cmax, maximum plasma concentration; CNS, central nervous system; cORR, confirmed overall response rate; EBC, early breast cancer; ET, endocrine therapy; HP, Herceptin + Perjeta; LMD, leptomeningeal disease; MBC, metastatic breast cancer; MTD, maximum tolerated dose; N/A, not applicable; pCR, pathologic complete response; PFS, progression-free survival; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor; Tx, treatment; 1L, first line; 2L, second line.

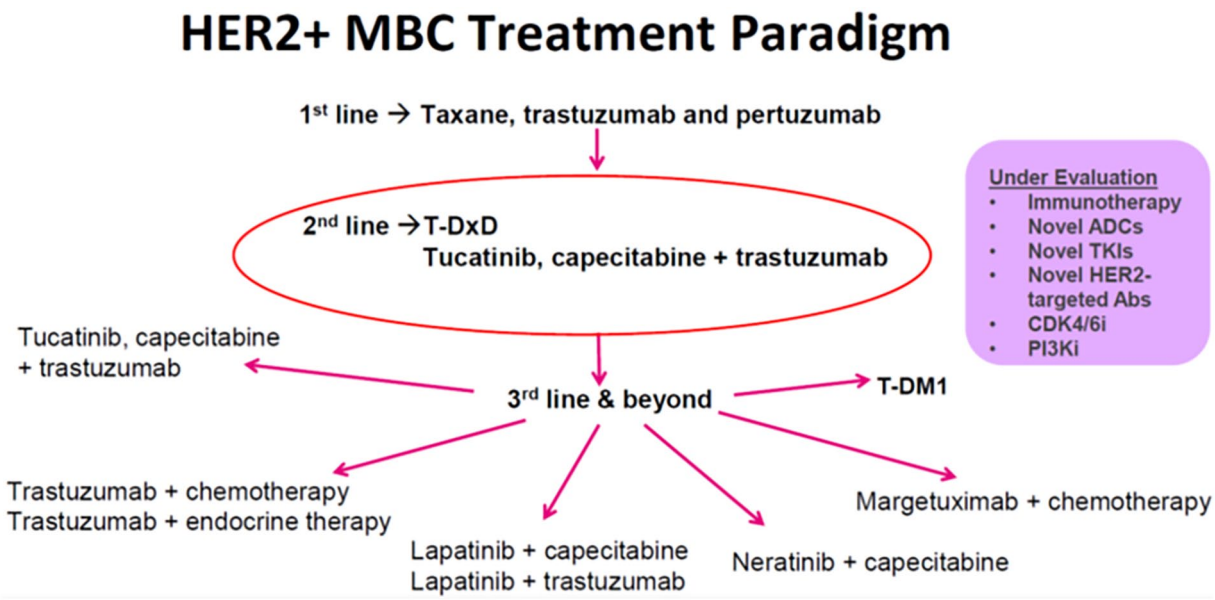

Figure 2. Treatment paradigm for HER2+ MBC. Abs indicates antibodies; ADCs, antibody-drug conjugates; CDK4/6i, cyclin-dependent kinase 4/6 inhibitors; MBC, metastatic breast cancer; PI3Ki, PI3K inhibitors; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab- deruxtecan; TKIs, tyrosine kinase inhibitors.

regimen of non-cross-resistant HER2-targeted treatments in *de novo* HER2+ MBC. The primary objective is to estimate the probability of enrollees being off anti-cancer treatment (except ET as applicable) and free of disease progression 4 years from study entry. Results from both trials will advance our knowledge regarding optimization of treatment strategies for HER2+ MBC.

Mechanisms of resistance to HER2-directed therapy

Patients with HER2+ MBC may live many years, and exceptional responders exist, particularly those with oligometastatic disease.[52] However, HER2+ MBC is usually incurable, and mOS is <5 years .[53] A barrier to improved OS is primary or acquired resistance to HER2-directed therapies (22%-25%).[54,55] Continued research focusing on unraveling novel and established mechanisms of resistance is ongoing; these include impaired drug binding to the HER2 receptor, which triggers compensatory mechanisms within the HER family (eg, HER3), including activation of different receptor tyrosine kinases (IGF-1R, MET), overactivity of the HER2 downstream signaling cascade (ie, the PI3K/AKT/mTOR pathway), and PTEN suppression.[56] Others include masking or loss of the HER2 epitope, HER2 heterogeneity, and host and tumor immunity.[57] Additional downstream pathways implicated in carcinogenesis include bidirectional crosstalk between HER2 and ER, and the cyclin D1-CDK4/Rb axis.[54] Reviews outlining resistance mechanisms to HER2-directed therapies are available elsewhere.[58]

Biomarkers

Given the evident heterogeneity of HER2+ MBC, clinically validated biomarkers could identify primary and acquired resistance to HER2-directed therapies, allowing better refinement of systemic therapy. However, biomarker discovery for HER2+ BC has been elusive. Currently, the use of HER2-targeted therapies is largely determined based on HER2 status. Hormone receptor (HR) expression is a notable biomarker as ~ 60% to 70% of HER2+ BC co-express HR and HER2, which modulates response to both HER2-directed and endocrine therapy due to "crosstalk" between the ER and HER2 pathways.[59] Combined HER2 and ER targeting can, therefore, be an effective treatment strategy in selected clinical settings.

Biomarkers evaluated to date include PIK3CA, HER2 co-ligands, PTEN, programmed death ligand 1 (PD-L1), tumor-infiltrating lymphocytes (TILs), and FcdeltaR polymorphisms.[60] Biomarkers most likely to inform prognostic stratification and treatment in the short to medium term include heterogeneity and quantification of HER2 levels, HER3 expression, intrinsic molecular subtypes (PAM50 analysis), DNA mutations, and other immune-related factors.[61] In CLEOPATRA, while HER2, HER3, and PIK3CA were prognostic, only HER2 accurately selected patients for trastuzumab + pertuzumab-based treatment in HER2+ MBC.[15] In EMILIA, T-DM1 was effective in both PI3KCA-mutated and wild-type tumors,[25] and in TH3RESA, a phase III trial of T-DM1 versus treatment of physician's choice in pretreated HER2+ MBC, T-DM1 prolonged mPFS in all biomarker subgroups analyzed.[62]

Future Directions

Novel HER2-targeted antibodies

Bispecific antibodies under evaluation in HER2+ MBC (Table 3) include zanidatamab, a HER2-targeted bispecific antibody that binds 2 nonoverlapping extracellular domains of

Table 3. Selected trials of HER2-directed therapies under investigation in HER2+ MBC (completed, ongoing and pending activation).

DRUG CLASS	MOA	NCT ± TRIAL NAME	TRIAL PHASE	TRIAL POPULATION	OTHER AGENT(S) UNDER EVALUATION	TRIAL OBJECTIVE (S)	TRIAL STATUS AND/OR RESULTS
HER2-targeted tyrosine kinase inhibitors (TKI) and antibody-drug conjugates (ADC)							
DZD1516	Oral, penetrable BBB, selective HER2 TKI	NCT04509596 DZD1516 in Combination With Trastuzumab and Capecitabine, or in Combination With T-DM1, in Patients With Metastatic HER2 Positive Breast Cancer	I	HER2+ MBC who have progressed on multiple therapies	DZD1516 + trastuzumab and capecitabine, or in combination with T-DM1	AEs, Dose Limiting Toxicities, Maximum Tolerated Dose, define Phase II combination dose	Active, Not recruiting. (n=21): 82.6% evaluable. Best response: SD in intra, extracranial and all lesions.[65]
Poziotinib	Irreversible pan-HER inhibitor	NCT02659514 Study of Poziotinib in Participants With HER2-Positive Metastatic Breast Cancer	II	HER2+-MBC post ⩾2 HER2-directed treatment regimens.	N/A	ORR	Completed ORR 26% or 27%; DCR 50% or 70%[66]
S-222611 Epertinib	Potent reversible inhibitor of HER2, EGFR and HER4	EudraCT Number: 2013-003894-87 A phase I/II study of epertinib plus trastuzumab with or without chemotherapy in patients with HER2-positive metastatic breast cancer	I/II	HER2-positive MBC	trastuzumab with or without chemotherapy (vinorelbine or capecitabine)	safety, tolerability, pharmacokinetics and antitumor activity	Completed ORR > 50% (epertinib + trastuzumab or chemotherapy); PR in CNS lesions (select patients)[67]
MRG002	ADC with humanized anti-HER2 IgG1 mAB conjugated to a microtubule inhibitor monomethyl auristatin E (MMAE).	NCT04924699 A Study of MRG002 in the Treatment of Patients With HER2-positive Unresectable Locally Advanced or Metastatic Breast Cancer	II/III	HER2+ MBC previously treated with trastuzumab (or a biosimilar) and anti-HER2-TKI	T-DM1	Phase II: evaluate the safety, efficacy, pharmacokinetics, and immunogenicity of MRG002 Phase III: safety and efficacy of MRG002 vs T-DM1	Recruiting
ARX788	ADC with humanized anti-HER2 mAB (IgG1κ) covalently conjugated to 2 microtubule-inhibiting payloads AS269	NCT04829604 ACE-Breast-03 ARX788 in HER2-positive, Metastatic Breast Cancer Subjects (ACE-Breast-03)	II	HER2+ MBC previously treated with T-DXd	N/A	ORR	Recruiting March 2023: PFS endpoint met[68]
DP303c	HER2-targeting ADC with a cleavable linker-MMAE payload.	NCT05334810 DP303c in Patients With HER2-positive Unresectable Locally Advanced, Relapsed, or Metastatic breast Cancer	II	HER2+-MBC	N/A	ORR	Not yet recruiting
Disitamab vedotin—RC48-ADC	HER2-targeting ADC comprised of hertuzumab coupling MMAE via a cleavable linker	NCT03500380 Study of RC48-ADC Administered Intravenously to Patients with HER2-Positive Metastatic Breast Cancer With or Without Liver Metastases	II/III	HER2+ MBC ± liver metastases	capecitabine + lapatinib	PFS	Recruiting
ZW49	ADC that combines a novel auristatin payload with anti-HER2 biparatopic antibody, ZW25, which binds trastuzumab and pertuzumab domains	NCT03821233 A Dose Finding Study of ZW49 in Patients With HER2-Positive Cancers	I	Locally advanced (unresectable) or metastatic HER2-expressing cancer	N/A	DLTs, AEs, lab abnormalities, EKG and LVEF abnormalities,, incidence of dose reductions	Active, not recruiting (ORR, 31% 95% CI, 15.3%-50.8%) PR rate of 31% and SD rate of 41%.[69] DLTs: G2 keratitis

(Continued)

Table 3. (Continued)

DRUG CLASS	MOA	NCT ± TRIAL NAME	TRIAL PHASE	TRIAL POPULATION	OTHER AGENT(S) UNDER EVALUATION	TRIAL OBJECTIVE (S)	TRIAL STATUS AND/OR RESULTS
FS-1502	ADC with a cleavable β-glucuronide linker and an antimitotic agent (monomethyl auristatin F)	NCT03944499 Phase 1 Study of FS-1502 in Patients with HER2 Expressed Advanced Solid Tumors and Breast Cancer NCT05755048 FS-1502 Versus T-DM1 for HER2-Positive Unresectable Locally Advanced or Metastatic Breast Cancer[70]	I III	HER2+ MBC, progressed on multiple therapies HER2+ MBC	N/A T-DM1	Efficacy endpoints: ORR, DCR, TEAEs PFS, OS, ORR	68-evaluable pts, best ORR 52.9% (36/68) (95% CI, 40.45-65.17) 2 CRs and 34 PRs Grade ⩾3 study-related TEAEs were reported in 27 (38.6%) pts, in which the most common events (⩾5%) were hypokalemia (18.6%), platelet count decreased (7.1%), and neutrophil count decreased (5.7%)[70] Not yet recruiting
SYD985 (Trastuzumab duocarmazine)	ADC with a cleavable linker-duocarmycin payload resulting in alkylation of the DNA in tumor cells.	NCT03262935 SYD985 vs Physician's Choice in Participants With HER2-positive Locally Advanced or Metastatic Breast Cancer (TULIP)	III	Progression during or after ⩾HER2-targeted treated for locally advanced or metastatic disease or progression during or after T-DM1	**N/A**	PFS	Completed median PFS was 7.0 mos. (95% CI, 5.4-7.2) with trastuzumab duocarmazine vs 4.9 mos. (95% CI, 4.0-5.5) with chemotherapy (HR, 0.64; 95% CI, 0.49-0.84; $P = .002$). median OS 20.4 mos. in the trastuzumab duocarmazine arm vs 16.3 months in the chemotherapy arm (HR, 0.83; 95% CI, 0.62-1.09; $P = .153$). Common AEs: conjunctivitis (38.2%), keratitis (38.2%), and fatigue (33.3%)[71]
PF-06804103	Anti-HER2 immunoglobulin G1 ADC comprising an anti-HER2 mAB conjugated with a cleavable linker to the cytotoxic agent Aur0101	NCT03284723 PF-06804103 Dose Escalation in HER2 Positive and Negative (Negative Only in Part 2) Solid Tumors	I	HER2 positive and negative advanced breast cancer	**N/A**	DLTs, AE, OR, DoR, PFS, TTP	Completed DLTs (mostly G3) occurred in 3 pts: arthralgia, neuropathy, myalgia, fatigue, and osteomuscular pain Preliminary ORR in patients treated with doses ⩾3 mg/kg was 52.4% (11/21).[72]
Bispecific antibodies							
ZW25 Zanidatamab	humanized, bispecific mAB directed against 2 domains of HER2 that are nonoverlapping	NCT02892123 Trial of ZW25 (Zanidatamab) in Patients With Advanced HER2-expressing Cancers NCT04276493 Anti-HER2 Bispecific Antibody ZW25 Activity in Combination With Chemotherapy With/Without Tislelizumab	I IB/II	HER2+ AST 1L HER2+ MBC	N/A N/A or docetaxel Tislelizumab Capecitabine oxaliplatin	DLTs, Lab Abnormalities or AEs ORR	Active, Not Recruiting ORR 86.4% (95% CI: 65.1, 97.1) The most common TEAEs were diarrhea (56.0%) and decreased neutrophil count (52.0%). Serious TEAEs occurred in 2 (8.0%) pts[73]
KN026	anti-HER2 bispecific antibody binds 2 nonoverlapping HER2 epitopes with dual HER2 signal blockade	NCT04778982 Study of KN026 in Combination With Palbociclib and Fulvestrant in Patients With Advanced Breast Cancer	II	HER2+ MBC	Palbociclib and Fulvestrant	DLT and ORR	Recruiting
TAC01-HER2	Immune Target: T-cell antigen coupler (TAC) CD3 and CD4 co-receptor domain Tumor Associated Antigen: HER2	NCT04727151 TAC T-cells for the Treatment of HER2-positive Solid Tumors (TACTIC-2)	I/II	HER2+ AST	fludarabine, cyclophosphamide	Incidence of TEAE at 24 months	Recruiting

(Continued)

Table 3. (Continued)

DRUG CLASS	MOA	NCT ± TRIAL NAME	TRIAL PHASE	TRIAL POPULATION	OTHER AGENT(S) UNDER EVALUATION	TRIAL OBJECTIVE (S)	TRIAL STATUS AND/OR RESULTS
IBI315	Immune Target: PDL1 Tumor Associated Antigen: HER2	NCT04162327 A Phase Ia/Ib Study of IBI315 in Patients With HER2-expressing Advanced Solid Tumors	I	HER2+ AST	N/A	AUC, Cmax, T1/2, Vd, Immune/correlatives	Recruiting
PRS-343	Immune Target: CD137 Tumor Associated Antigen: HER2 targets HER2 and costimulatory immune receptor 4-1BB on T cells.	NCT03650348 PRS-343 in Combination With Atezolizumab in HER2-Positive Solid Tumors	I	HER2+ AST	atezolizumab	DLTs and RP2D	Recruitment status unknown No DLT most frequent TEAEs: infusion-related reactions (25%), nausea (7%), arthralgia (5%), vomiting (4%), chills (4%), and fatigue (4%).[74]
SAR-443216	Immune Target: CD3/CD28 Tumor Associated Antigen: HER2 trispecific antibody with binding sites for HER2, CD3 and CD28, and contains a mutated IgG4-Fc which lacks effector function	NCT05013554 Dose Escalation and Expansion Study of SAR443216 in Participants With Relapsed/Refractory HER2 Expressing Solid Tumors	I	HER2+ AST	N/A	MTD, safety (IV or SC administration)	Recruiting[75]
NJH395	Immune Target: TLR7 Tumor Associated Antigen: HER2 Antibody-mediated delivery of TLR7 may limit systemic toxicities and promote long-lasting antitumor immune response	NCT03696771 Study to Determine Safety and Dose of NJH395 in Non-breast HER2+ Advanced Cancer	I	HER2+ AST	N/A	Safety	most common ⩾G3 AEs lymphopenia (27.8%) and increased AST (11.1%) No CR/PR; 9 = SD[76]
BDC-1001	Immune Target: TLR7/8 Tumor Associated Antigen: HER2	NCT04278144 A First-in-human Study Using BDC-1001 as a Single Agent and in Combination With Nivolumab in Advanced HER2-Expressing Solid Tumors	I/II	HER2+ AST	Phase 1: N/A Phase 2: nivolumab	Part 1: MTD, RP2D Part 2: combination with nivolumab to determine MTD, R2PD	Recruiting[77]
SBT6050	Immune Target: TLR7/8 Tumor Associated Antigen: HER2	NCT04460456 A Study of SBT6050 Alone and in Combination With PD-1 Inhibitors in Subjects With Advanced HER2 Expressing Solid Tumors	I	HER2 expressing/amplified AST	Pembrolizumab Cemiplimab	DLTs	Active, not recruiting PR (n = 1), SD (n = 3), and PD (n = 10). most frequent (>25%) related TEAEs were chills, diarrhea, fatigue, hypotension, injection-site reaction, nausea, pyrexia, and vomiting.[78]
HER2 Bi–aATCs/HER2BATs	Immune Target: CD3+ activated T cells Tumor Associated Antigen: HER2	NCT03272334 Her2-BATS and Pembrolizumab in Metastatic Breast Cancer (Breast-47)	I/II	MBC (including HER2+)	HER2 BATs with Pembrolizumab	DLTs	Recruiting No DLTs median OS 36.2 mos. for all pts, 57.4 mos. for HER2 3+ pts, and 27.4 mos. for HER2 0–2+ pts.[79]
Runimotamab/BTRC4017A	Immune Target: CD3 Tumor Associated Antigen: HER2	NCT03448042 A Study of Runimotamab in Participants With Locally Advanced or Metastatic HER2-Expressing Cancers	I	HER2+ AST	trastuzumab	Safety, tolerability, PK	Recruiting

(Continued)

Table 3. (Continued)

DRUG CLASS	MOA	NCT ± TRIAL NAME	TRIAL PHASE	TRIAL POPULATION	OTHER AGENT(S) UNDER EVALUATION	TRIAL OBJECTIVE (S)	TRIAL STATUS AND/OR RESULTS
ACE1702	Immune Target: NK cells Tumor Associated Antigen: HER2	NCT04319757 ACE1702 in Subjects With Advanced or Metastatic HER2-expressing Solid Tumors	I	HER2+ AST	Cyclophosphamide fludarabine	DLTs, SAEs	Recruiting
DF1001	Immune Target: NK cells Tumor Associated Antigen: HER2	NCT04143711 Study of DF1001 in Patients With Advanced Solid Tumors	I/II	HER2+ AST	Phase 1: n/a Phase 2: n/a	Nivolumab Nab-paclitaxel	Recruiting
Targeted Therapies (CDK4/6 inhibitors, PARP inhibitors, PIK3CA inhibitors, Checkpoint Inhibitors, Others)							
Palbociclib	CDK 4/6 inhibitor	NCT02947685 Randomized, Open Label, Clinical Study of the Targeted Therapy, Palbociclib, to Treat Metastatic Breast Cancer (PATINA) NCT02448420 Study of Palbociclib and Trastuzumab With Endocrine Therapy in HER2-positive Metastatic Breast Cancer (PATRICIA II)	III II	ER+ HER2+ MBC ER+ HER2+ MBC (Luminal IS by PAM50; postmenopausal)	Anti HER2 therapy and ET trastuzumab ± letrozole Cohort C1: trastuzumab + ET Cohort C2: TPC	PFS PFS at 6 months	Active, Not recruiting Recruiting
Ribociclib	CDK 4/6 inhibitor	NCT02657343 An Open-Label, Phase Ib/ II Clinical Trial Of Cdk 4/ 6 Inhibitor, Ribociclib (Lee011), In Combination With Trastuzumab Or T-Dm1 For Advanced/ Metastatic Her2-Positive Breast Cancer. NCT05319873 Ribociclib, Tucatinib, and Trastuzumab for the Treatment of HER2 Positive Breast Cancer	I/II Ib/II	HER2+ MBC HER2+ MBC (HER2+ EBC-neoadjuvant patients included in PhII)	Trastuzumab Or T-DM1 Tucatinib + trastuzumab	RP2D, CBR Phase 1 dose escalation: Safety; RP2D of ribociclib	Completed Recruiting
Abemaciclib	CDK 4/6 inhibitor	NCT02675231 A Study of Abemaciclib (LY2835219) in Women With HR+, HER2+ Locally Advanced or Metastatic Breast Cancer (monarcHER)	II	HER2+ MBC	Abemacicib + trastuzumab vs abemaciclib, trastuzumab + fulvestrant vs SOC chemotherapy	PFS	Active, not recruiting median PFS between group A (8.3 months) and group C (5.7 months; $P = .051$).[80]
Ipatasertib	Small molecule inhibitor of AKT (component of PI3K/AKT pathway)	NCT04253561 Ipatasertib + Pertuzumab + Trastuzumab in Advanced HER2+ PI3KCA-mutant Breast Cancer Patients (IPATHER)	IB	HER2+ MBC with PIK3CA mutation with maintenance HP after 1L treatment for metastatic disease with a taxane plus trastuzumab and pertuzumab	trastuzumab + pertuzumab	RP2D	Recruiting
Alpelisib	PIK3CA inhibitor	NCT04208178 Study of Alpelisib (BYL719) in Combination With Trastuzumab and Pertuzumab as Maintenance Therapy in Patients With HER2-positive Advanced Breast Cancer With a PIK3CA Mutation (EPIK-B2)	III	HER2+ MBC with PIK3CA mutation after 1L treatment for metastatic disease with a taxane plus trastuzumab and pertuzumab	Trastuzumab and Pertuzumab	Part 1: DLTs Part 2: PFS	Recruiting
PARP Inhibitors Niraparib	PARP inhibitor	NCT03368729	I/II	HER2+ MBC, 2L+ therapy	Trastuzumab	Phase I: DLT Phase II: ORR	Recruiting

(Continued)

Table 3. (Continued)

DRUG CLASS	MOA	NCT ± TRIAL NAME	TRIAL PHASE	TRIAL POPULATION	OTHER AGENT(S) UNDER EVALUATION	TRIAL OBJECTIVE (S)	TRIAL STATUS AND/OR RESULTS
Vaccines							
Dendritic Cell (DC1) Vaccine	May elicit CD4+ HER2-specific T-cell responses. HER2-specific T cells are expanded ex vivo which will be infused to patients subsequently following lymphodepletion therapy with cyclophosphamide. Trastuzumab and pepinemab will be given as maintenance in addition to booster DC1 vaccines	NCT05378464 Adoptive T Cell Therapy Following HER2-Pulsed Dendritic Cell Vaccine & Pepinemab /Trastuzumab in Patients w/ Metastatic HER2+ Breast Cancer	I	HER2+ MBC, Progression on trastuzumab, ⩽3 lines of therapy in metastatic setting	Trastuzumab Pepinemab T-Cell therapy	MTD	Recruiting
DC1 vaccine	DCs loaded with HER2 ICD	NCT00005956 HER2 ICD DC vaccine vs DC vaccine containing tetanus/CMV control for pts with stage II–IV HER2+ BC post surgery	Pilot	pts with stage II-IV HER2+ BC post surgery	N/A	Safety at 12 months	Completed well-tolerated significant immunogenicity 100% 4.5-year OS.[81]
DNA-Based Vaccine	pNGVL3-hICD HER2 ICD DNA plasmid-based vaccine	NCT02061332	I	stage III/IV HER2+ BC in remission/stable bone-only metastases, treated with intradermal plasmid-based vaccine	N/A	safety and immunogenicity	Completed Immunization with the 100-μg dose was associated with generation of ERBB2-specific type 1 T cells[82]
Whole Cell–Based Vaccines	HER2+, GM-CSF secreting Vaccine Allogeneic, HER2+ GM-CSF secreting Breast tumor vaccine	NCT00093834	I	HER2+ MBC	Trastuzumab + cyclophosphamide	Toxicity, immune responses	Completed HER2-specific immunity detected. PFS 7 mos.; OS 42 mos.[83]
Peptide/ Protein-Based Vaccines	Recombinant protein (ECD and a fragment of the ICD combined with adjuvant AS15)	NCT00952692	I/II	trastuzumab-refractory HER2+ MBC	lapatinib		Completed Median TTP: 55 days 300 day OS 92%.[84]
	MVF-HER-2 (597-626)-MVF-HER-2 (266-296) 2 chimeric HER2 B-cell peptide vaccines incorporating a "promiscuous T-cell epitope."	NCT01376505	I	AST, including HER2+ MBC	N/A	Safety and toxicity of immunization, optimum immunologic/ biological dose of combination HER2 vaccines, measure humoral and cellular immune responses,	Completed Most common related toxicity: injection-site reactions (24%). 2 pts had a PR, 14 had SD.[85]
	HER2+, GM-CSF secreting Vaccine Allogeneic, HER2+ GM-CSF secreting Breast tumor vaccine	NCT00399529	II	MBC (HER2+ MBC pts included)	chemotherapy	AEs, CBR	Completed HER2-specific T helper dependent immunity and ab responses detected.[86]

(Continued)

Table 3. (Continued)

DRUG CLASS	MOA	NCT ± TRIAL NAME	TRIAL PHASE	TRIAL POPULATION	OTHER AGENT(S) UNDER EVALUATION	TRIAL OBJECTIVE (S)	TRIAL STATUS AND/OR RESULTS
Virus-Based Vaccines AVX901	Antigen-specific cancer vaccine represented by virus-like replicon particle (VRP)-HER2	NCT01526473 A Phase I Study To Evaluate The Antitumor Activity And Safety Of AVX901	I	HER2+ AST	N/A	Safety	Completed No results posted
VRP-HER2 Vaccination	Increases HER2-specific memory CD8 T cells with antitumor effects	NCT03632941 A Study to Evaluate Concurrent VRP-HER2 Vaccination and Pembrolizumab for Patients With Breast Cancer	II	HER2+ MBC	Pembrolizumab	Number of Tumor infiltrating Lymphocytes and HER2 specific antibodies	Active, Not Recruiting No results available
Immunotherapy							
Pembrolizumab	PD-1 Inhibitor	NCT02129556 Anti-PD-1 Monoclonal Antibody in Advanced, Trastuzumab-resistant, HER2-positive Breast Cancer (PANACEA)	I/II	Trastuzumab-resistant, HER2+ MBC	Trastuzumab	DLT, ORR	Completed Six (15%) of 40 PD-L1+ pts achieved an objective response. No objective responders among the PD-L1- pts. Most common SAEs: dyspnea (n=3 [5%]), pneumonitis (n=3 [5%]), pericardial effusion (n=2 [3%]), and upper respiratory infection (n=2 [3%]).[87]
Atezolizumab	PD-L1 Inhibitor	NCT02924883 A Study to Evaluate the Efficacy and Safety of Trastuzumab Emtansine in Combination With Atezolizumab or Atezolizumab-Placebo in Participants With Human Epidermal Growth Factor-2 (HER2) Positive Locally Advanced or Metastatic Breast Cancer (BC) Who Received Prior Trastuzumab and Taxane Based Therapy (KATE2)	II	HER2+ MBC who Received Prior Trastuzumab and Taxane Based Therapy	T-DM1	PFS, AEs	Completed Median PFS 8.2 months (95% CI, 5.8-10.7) in atezolizumab arm vs 6·8 mos. (4.0-11.1) for placebo (HR, 0.82, 95% CI, 0.55-1.23; *P*=.33). SAEs in 43 (33%) of 132 pts in atezolizumab arm and 13 (19%) of 68 pts who received placebo.[88]
CT-0508	CAR-macrophages	NCT04660929 CAR-macrophages for the Treatment of HER2 Overexpressing Solid Tumors	I	all HER2 overexpressing solid tumors	Pembrolizumab	Safety	Recruiting

Abbreviations: ADC, antibody-drug conjugate; AE, adverse events; AST, advanced solid tumors; BAT, bispecific antibody armed activated T cells; BBB, blood-brain barrier; CBR, clinical benefit rate; CI, confidence interval; CNS, central nervous system; CR, complete response; DCR, disease control rate; DLT, dose limiting toxicities; DoR, duration of response; ER+, estrogen receptor positive; ET, endocrine therapy; G, grade; HR, hazard ratio; IS, intrinsic subtype; L, line; LVEF, left ventricular ejection fraction; mAB, monoclonal antibody; MBC, metastatic breast cancer; mos., months; MMAE, monomethyl auristatin E; MTD, maximum tolerated dose; OR, overall response; ORR, objective response rate; OS, overall survival; PD, progressive disease; PD1, programmed death; PDL1, programmed death ligand 1; PFS, progression-free survival; Ph, phase; PK, pharmacokinetics; PR, partial response; RP2D, recommended phase 2 dose; SAE, serious adverse events; SD, stable disease; SOC, standard of care; T-DM1, ado-transtuzumab emtansine; T-DXd, fam-transtuzumab deruxtecan; TEAE, treatment-emergent adverse events; TKI, tyrosine kinase inhibitor; TPC, treatment of physicians choice; TTP, time to progression.

HER2 (ECD4 and ECD2) and KN026, which simultaneously binds 2 distinct HER2 epitopes.[63] In a phase 1b/2 trial (NCT04276493), zanidatamab + docetaxel was tolerable and active in 1L HER2+ MBC (ORR, 86.4%; 95% CI, 65.1-97.1). In another trial evaluating zanidatamab + palbociclib + fulvestrant in pretreated HR+ HER2+ MBC, responses were seen in most participants (NCT04224272). Furthermore, in a phase I trial in HER2+ MBC, KN026 was well tolerated, with an ORR of 28.1% and mPFS of 6.8 months.[64] Interestingly, co-amplification of HER2/CDK12 may select patients who benefit most. Bispecific antibodies which simultaneously target both HER2 and various immune targets are also under clinical evaluation (Table 3) and are discussed in the section on novel immunotherapies.

Novel HER2-targeted ADCs

HER2-directed ADCs are key immune-targeted strategies, which increase cytotoxicity while reducing chemotherapy off-target AEs due to antibody-driven drug internalization. Compared with treatment of physicians choice, trastuzumab duocarmazine (SYD985) significantly improved PFS in HER2+ MBC after 2L+ of MBC therapy. Ocular toxicity was the most common AE, and ILD was observed in a small percentage of patients.[71] ARX788 is a novel ADC targeting HER2 with a different payload and use of microtubule inhibitor against cell lines resistant to T-DM1 with induction of greater apoptotic events.[89,90] The phase III ACE-Breast-02 trial recently met its PFS endpoint.[68] Therefore, the global ACE-Breast-03 trial (NCT04829604) is ongoing in patients pretreated with T-DXd and tucatinib. Other ADCs under clinical evaluation include disitamab vedotin (RC48-ADC), MRG002, ZW49, and PF-06804103 (Table 3).

Novel HER2-targeted TKIs

HER2-targeted TKIs in development include DZD1516, poziotinib, and epertinib (S-222611) (Table 3). DZD1516 is a highly selective TKI with full BBB penetrance and very high HER2 selectivity that was evaluated in a phase I trial in HER2+ MBC.[65] Of 19 (82%) evaluable patients, stable disease was the optimal response. Combination therapy and evaluation in earlier treatment lines is planned.

Novel combination strategies

Combination therapies have been evaluated in HER2+ MBC, whereby HER2 is not the only target. Agents studied, or under study, include novel HER2-targeted TKIs,[65] CDK4/6 inhibitors (CDK4/6i),[91] PI3K inhibitors (PI3Ki),[92,93] and PARP inhibitors (PARPi).[94] Specifically, there was preclinical and clinical data to support further study of CDK4/6i,[91] PARPi,[94] and PI3Ki[92] in HER2+ MBC. These agents can be combined with HER2-targeted therapy ± ET, often without chemotherapy. Ongoing and reported trials are shown in Table 3.

CDK4/6i

There is strong rationale for combining CDK4/6i with HER2-targeted therapies. In MONARCHER, patients with HR+ HER2+ MBC who had received ⩾2 HER2-directed therapies were randomized 1:1:1 to abemaciclib, trastuzumab, and fulvestrant (A), abemaciclib and trastuzumab (B), and trastuzumab with investigators choice of chemotherapy (C). A 2.6-month PFS advantage in arm A versus arm C (8.3 mos. vs 5.7 mos. $P = .051$) was noted.[80] However, in 2022 evaluation of abemaciclib in HER2+ MBC was discontinued. PATINA (NCT02947685) is evaluating palbociclib + HER2-directed therapy + ET versus standard therapy as 1L treatment for HR+ HER2+ MBC; results are expected shortly. PATRICIA (NCT02448420) showed that palbociclib + trastuzumab is active and safe in trastuzumab pretreated ER+/HER2+ (PAM50 Luminal A or B subtype).[95] As enrollment was stopped prematurely, a new randomized cohort aims to recruit 102 patients with HER2+/HR+ PAM50 Luminal A or B tumors.[96]

PARPi

Preclinical data show that HER2+ BCs are sensitive to PARP inhibition independent of sensitivity to HER2-targeted therapies.[94] The premise behind TBCRC50 (A phase 1B/2 study of the PARPi niraparib + trastuzumab in patients with HER2+ MBC; NCT03368729) is that HER2+ BC resistant to HER2-targeted therapies is sensitive to PARP inhibition mediated by the canonical NFκB signaling pathway, increasing cell death and treatment response. TBCRC50 is enrolling patients with HER2+ MBC (2L-5L setting).

PI3K inhibitors

Mutations in PIK3CA co-occur with HER2-amplification in ~20% of cases.[92] Therefore, PI3Ki+ HER2-directed therapy were evaluated for the treatment of PIK3CA-mutated HER2+ MBC. However, early phase studies showed that addition of pan-PI3Ki to HER2-targeted therapies caused treatment-limiting side effects.[93] The α-specific PI3Ki alpelisib + T-DM1 was active and tolerable in persons with trastuzumab-resistant HER2+ MBC.[97] Phase III studies are required to assess the efficacy of adding α-specific PI3Ki to HER2-targeted therapies.

Immune-based therapies

The role of immunotherapy in HER2+ BC is relevant given the presence of higher stromal TILs, which infer immunogenic potential.[98] Therefore, novel HER2-directed mAbs, ADCs, vaccines, and adoptive T-cell therapies are being evaluated. Other immune-based therapies which have/are being studied include checkpoint inhibitors (CPIs), bispecific antibodies, and immune-stimulator Ab conjugates (ISACs). Most drug development efforts are focusing on ADCs and immunotherapies

currently. Table 3 shows results of ongoing and completed studies, including AEs and safety data, for CPIs, HER2-targeted vaccines, bispecific antibodies, and other immune-based therapies.

Immune checkpoint inhibitors

Combining HER2-directed therapy and CPI in HER2+ MBC has shown modest results (Table 3). Results from PANACEA, whereby patients with heavily pretreated HER2+ MBC received trastuzumab + pembrolizumab showed limited responses; however, ORR was better in patients with PD-L1+ disease. It was advised that further studies should focus on PD-L1+ patients with less heavily pretreated HER2+ MBC.[87] In KATE2, 202 participants were randomized 2:1 to T-DM1 and atezolizumab versus T-DM1 and placebo. PFS was improved by ~4 months in patients with PD-L1+ status.[88] Rates of grade 3-5 AEs were similar between arms with a recommendation to focus on patients with PD-L1+ HER2+ MBC.[88] In the NRG-BR004 trial (NCT0319988), patients with treatment-naïve HER2+ MBC were randomized to 1L THP + atezolizumab versus THP and placebo. Due to toxicity and accrual concerns, the study prematurely closed in 2022. Follow-up continues to assess PFS, OS and monitor for delayed immune AEs.[99]

HER2 targeted vaccines

Therapeutic cancer vaccines aim to treat existing malignancies by improving the antitumor immune response.[100] Several types of HER2 vaccinations are in clinical development; ongoing trials in HER2+ MBC are evaluating adoptive T-cell therapy, plasmid-based DNA vaccines, and others (peptide, protein, cell-based, and dendritic cell vaccines) (Table 3). Interestingly, in a phase I study (NCT00436254) of a plasmid DNA vaccine (n = 66), mOS was not reached at almost 10 years for patients with stage III/IV HER2+ MBC[101] (mOS 4.7 years in CLEOPATRA).[30]

Other immune-based therapies

Immune-stimulator antibody conjugates (ISAC) combine tumor-targeting monoclonal antibodies with immunostimulatory agents to enable targeted delivery of immune activators into tumors (Table 3). NJH395 is a novel, first-in-class ISAC (toll-like receptor 7 agonist conjugated to a HER2-targeted antibody via a noncleavable linker payload).[102] In a phase 1 study in non-breast HER2+ metastatic cancers (n = 18), cytokine release syndrome was common, but manageable. However, antidrug antibodies and neuroinflammation posed a clinical challenge.[76] BDC-1001 is a HER2-targeted ISAC which triggers local activation of the innate immune system and generates a durable tumor-targeted adaptive immune response. In a phase 1/2 study of BDC-1001 ± nivolumab in advanced HER2+ solid tumors, the combinations were overall well tolerated, and clinical activity was noted (5 partial responses and 10 stable disease ⩾ 6 months). Further development of BDC-1001 with phase 2 expansion in HER2-expressing solid tumors at the RP2D is planned.[103] CAR-M and CAR-NK therapies, bispecific engagers, engineered toxin bodies, HER2-targeted proteolysis-targeting chimeras (PROTACs), and targeted thorium-227 conjugates are also under study; some of these agents are in clinical development (Table 3).

Special considerations: brain metastasis/ leptomeningeal disease

Durable treatment options for HER2+ BCBM and leptomeningeal disease remain limited. Therefore, improving prevention strategies and treatment options is critically important. The incidence of CNS metastases as a first site of recurrence is <10% (2.2% at 4-year median follow-up in the HERA trial).[104,105] Unfortunately, in adjuvant trials of pertuzumab and T-DM1, there was no reduction in the incidence of BCBM in the treatment versus control arms.[106,107] Multidisciplinary management is key, as treatment options must be individualized in terms of local regional and systemic therapy. Regarding systemic therapy, an exploratory analysis from CLEOPATRA showed a longer median time of first site of CNS metastasis in the pertuzumab arm (15.0 vs 11.9 months, HR, 0.58, 95% CI, 0.39-0.85), which infers that despite reported low BBB permeability, mAbs have a role in 1L treatment of HER2+ MBC with BM.[108] More recently approved HER2-targeted therapies better penetrate the BBB (Table 4); the strongest data for CNS efficacy are for tucatinib and T-DXd.[109] In HER2CLIMB (291 patients with BCBM), the addition of tucatinib resulted in a CNS ORR of 47.3%, mPFS of 9.9 months, and an OS of 18.1 months.[20] In the T-DXd arm of DB03, subgroup analysis CNS response rates were impressive (67.4% CNS-ORR and mPFS of 15 months with T-DXd vs 20.5% and 3 months with T-DM1).[45] Furthermore, the prospective, single-arm, phase II TUXEDO-1 trial evaluated T-DXd in 15 patients with HER2+ active BCBM. In the intention-to-treat population, intracranial RR was 73.3% (11/15), and at 11 months median follow-up, PFS was 14 months.[110] Whether tucatinib and/or T-DXd can prevent BCBM is being evaluated in postneoadjuvant trials (Destiny-Breast05 [NCT04622319], A011801 [NCT04457596]). To ensure further progress, careful clinical trial design is required, including further studies of HER2-targeted TKIs, ADCs, and HER2 mAbs with optimal BBB penetrance. Furthermore, trials including relevant CNS endpoints, patient-reported outcomes, and a focus on BCBM prevention are needed. Novel preclinical models will provide detailed information regards the mechanistics of CNS tropism, the BBB, and the brain-tumor microenvironment.[111] Novel drugs, combinations, and targets (ie, BM-specific genomics, immunotherapy, HER2 CAR T-cells) are being studied. When

Table 4. Efficacy of systemic therapy for HER2-positive BCBM.

HER2-DIRECTED AGENT	DATASET OR TRIAL	N	SYSTEMIC THERAPY	RANDOMIZED (Y/N)	CNS ORR (%)	MPFS (MONTHS)	MOS (MONTHS)
T-DM1	Fabi et al[112]	70	T-DM1	N	24.5	7	14
T-DXd	Destiny-Breast 01[113] Destiny-Breast 03[45]	24 82	T-DXd T-DXd vs T-DM1	N Y	50 63.4 vs 20	18.1 15.1 vs 3	- -
Lapatinib	Pooled dataset[114]	799	Lapatinib + capecitabine	n/a	29.2	4.1	11.2
Tucatinib	HER2CLIMB[22] HER2CLIMB -02[42]	291 90	Tucatinib + capecitabine + trastuzumab vs placebo + capecitabine + trastuzumab Tucatinib + T-DM1 vs Placebo + T-DM1	Y Y	47.3 vs 20 -	13.9 vs 5.6 7.8 vs 5.7	21.6 vs 12.5
Neratinib[6]	TBCRC022[115]	49	Neratinib + capecitabine Neratinib + T-DM1	N N	49 (no prior lapatinib) 33 (prior lapatinib) 33.3 (cohort A-untreated BCBM) 29.4 (cohort B-T-DM1 naive) 28.6 (cohort C-prior T-DM1)	5.5 13.3 - -	3.1 15.1
Pyrotinib	PERMEATE[116]	78	Pyrotinib + capecitabine	N	74.6 (RT naïve) 42.1 (prior RT)	11.3 5.6	- -

Abbreviations: BCBM, breast cancer brain metastases; N, no; n/a, not applicable; RT, radiation therapy; T-DM1, ado trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; Y, yes.

possible, oncologists should enroll patients on clinical trials, including those with progressive/untreated BCBM.

Conclusions

Major progress has been made in the treatment of HER2+ MBC with the emergence of multiple targeted agents that improve PFS and OS, and possibly cure selected patients. However, challenges remain, namely, overcoming therapeutic resistance, optimal sequencing of therapies (and use of immune-based therapies), therapy (de)escalation, and the effective prevention and treatment of BCBM. Exploiting the potential of novel therapies and identifying predictive biomarkers will be crucial to ensure continued progress. Innovative research strategies addressing the aforementioned challenges will undoubtedly drive further accomplishments in the field.

Declarations

Ethics approval and consent to participate

Not Applicable

Consent for publication

Not Applicable

Author contributions

Sarah K Premji: Conceptualization; Investigation; Methodology; Visualization; Writing—original draft; Writing—review & editing.

Ciara C O'Sullivan: Conceptualization; Investigation; Methodology; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing.

Acknowledgements

Not Applicable

Availability of data and materials

Not applicable

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