Anti-HER2-targeted therapies for the treatment of advanced HER2-positive breast cancer with brain metastases (Review)

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Abstract. Compared with other metastatic sites, breast cancer brain metastases (BCBMs) are associated with the shortest survival time. In addition, human epidermal growth factor receptor 2 (HER2) is observed to be amplified in 20-25% of breast cancer cases where it is a poor prognostic factor for brain metastases. Various anti-HER2 targeted therapies have brought both new opportunities and challenges to patients with HER2-positive BCBM over the past decade. However, prolonging survival time and improving quality of life of patients have become controversial issues in the field of clinical research on BCBMs. On the basis of the latest literature, the present review documents the anti-HER2 targeted drugs applied in patients with HER2-positive BCBM. Further studies on the efficacy and safety of novel HER2-targeted drugs and combined or sequential therapy in clinical treatment are expected to provide more effective strategies for the treatment of patients with HER2-positive BCBM.

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1. Introduction

In adult patients with cancer, brain metastases (BMs) most commonly originate from the lungs, breast, skin (melanoma) and gastrointestinal tract (1). Breast cancer (BC) is the second most common primary malignancy that is prone to BMs, which occurs in ~17% patients (2). In addition, the probability of BM is greater in human epidermal growth factor receptor 2 (HER2)-positive BC compared with that in other BC subtypes, ranging 30-55% (3). Breast cancer with brain metastases (BCBM) typically occurs at advanced stages (4,5), where the median survival time is <6 months (4,6-8).

Currently, the main treatment for BCBM (9) is local treatment, including surgery and radiotherapy. For single and large metastases, surgery can quickly relieve symptoms. However, the risk of developing leptomeningeal seeding from surgery is high, requiring comprehensive assessment of the patient and tumor status (10). The types of radiotherapy that can be applied for BCBM can be categorized into whole-brain radiotherapy (WBRT) or stereotactic radiotherapy (SRS). WBRT attempts to treat multiple metastases, but may cause cognitive impairments (11). By contrast, SRS is more precisely positioned and can cause significant oncolytic effects on small metastases with less damage, but it is inferior when targeting large metastases or multiple metastases (12). Reported overall survival (OS) in patients with breast cancer after treatment with either WBRT alone or SRS was 4-8 and 13-16 months previously found to be (3,13), respectively. In the retrospective study (14), which analyzed the data of 873 BCBM patients from 1999 to 2012, the median overall survival (OS) after diagnosis of BM was 9.1 months. By contrast, the OS of patients receiving WBRT was prolonged compared with those who had not received any treatment (95% CI, 0.52-0.88; P=0.004). Comparison in OS between SRS alone and surgery or SRS followed by WBRT (S/SRS + WBRT) yielded no difference (median OS, 14.9 vs. 17.2 months) (14).

In addition, with improvements in systemic therapy efficacy and the rapid development of imaging techniques, the incidence of BCBM has increased in recent years (15,16).

Systemic therapy has led to significant survival benefit in HER2-positive BCBMs, but due to the blood-brain barrier (BBB), which partially excludes macromolecules from the CNS compartment, it serves the main role in the control of the extracranial disease. In addition, the use of imaging techniques contributed to improvements in detection rate of BM (17). The present review aims to discuss the current anti-HER2 targeted systemic therapies for patients with HER2-positive BCBMs on the basis of the latest literature (Table I).

2. Monoclonal antibodies (mAbs)

mAbs can bind not only to extracellular receptors but also to its epitope (18). They can block growth factor receptors, effectively preventing cell proliferation and indirectly recruiting cytotoxic cells, such as monocytes and macrophages, to mediate antibody-dependent cell-mediated cytotoxicity (ADCC) (19). Monoclonal antibodies can also bind to complement, leading to a type of toxicity known as complement-dependent cytotoxicity (CDC).

Trastuzumab (Herceptin). Trastuzumab, a humanized mAb, was the first drug approved for the treatment of HER2-positive metastatic BC (20). Trastuzumab mediates ADCC, inhibits the PI3K/AKT signaling pathway, blocks the G_1 phase of the cell cycle and inhibits DNA damage repair to serve an antitumor role (21,22). It is considered that the BBB allows substances of only small molecular weight (400-500 Da) (23) to pass through. Because of its large molecular mass (148,781 Da), trastuzumab is considered to be unable to cross the intact BBB. However, intracranial trastuzumab uptake and reduced BM have been observed in animal models of HER2-positive BCBM (24). The addition of trastuzumab to first-line treatment for HER2-positive metastatic disease has been documented to significantly increase the time to central nervous system (CNS) metastasis (25). The possible causes include disruption of the BBB during BM or after radiotherapy, in addition to increased vascular permeability due to neovascularization and the secretion of vascular endothelial growth factor (VEGF) (26). With tumor cell proliferation and new blood vessel formation, the blood-tumor barrier (BTB) forms between the tumor and blood vessels, where BTB permeability is significantly increased compared with the BBB. Therefore, some drugs that have difficulty passing through the BBB can enter brain metastases through intercellular bypass (27).

The registHER trial (28) previously demonstrated that patients with BM (n=258) who received trastuzumab after being diagnosed with CNS metastases had significantly longer OS compared with those who did not [n=119; 17.5 vs. 3.7 months, hazard ratio (HR)=0.25]. In addition, trastuzumab treatment (HR=0.33; 95% CI, 0.25-0.46; P=0.001) was found to be independently associated with a reduced risk of mortality after CNS metastasis. However, because of the low intracranial concentration of trastuzumab, these OS benefits were proposed to be due mainly to the long-term control of the extracranial disease (20).

At present, attempts have been made of using various biological techniques to increase drug permeability with the purpose of increasing the intracranial concentration of trastuzumab, such as combining MRI-guided focused ultrasound (MRgFUS) (29) with trastuzumab. MRgFUS was found to enhance drug uptake in 87±17% of sonicated voxels (>20% increase in standardized uptake value ratio), with ≤450% voxel-wise increase detected. In addition, nanoparticles can be used as carriers for macromolecular drugs to cross the BBB (30). However, the efficacy of nanoparticles remains in the experimental stage and there is no specific data.

Pertuzumab (Perjeta). Pertuzumab is a recombinant humanized mAb that can binds to subdomain II of the extracellular domain of HER2, blocking the dimerization of HER2 with HER3 and HER2 with HER1, which inhibits the downstream PI3K and MAPK pathways (31). It also exhibits a complementary mechanism with trastuzumab, resulting in dual obstruction when used in combination (32). According to the CLEOPATRA trial results (33), the time to CNS progression was found to be delayed with pertuzumab (15 vs. 11.9 months; P=0.0049) (34), which may be due to the superior control of extracranial disease with pertuzumab. In a retrospective study (35), the combination of pertuzumab and trastuzumab significantly improved the OS to 44 months, compared with that after other-HER2-targeted therapy (17 months) and no-HER2-targeted therapy (3 months) in patients with HER2-positive BCBM. In addition, the PATRICIA study (36) showed that pertuzumab combined with high-dose trastuzumab (6 mg/kg weekly) achieved a CNS objective response rate (ORR) of only 11% (95% CI, 3.0-25.4, median duration of response, 4.6 months). However, a large proportion of patients achieved clinical benefit at 4 (68%) and 6 months (51%). Notably, two patients had stable intracranial and extracranial disease for >2 years. In the final efficacy analysis based on the latest follow-up, the median CNS-progression-free survival (PFS) was found to be 4.6 months, whereas the systemic PFS was also 4.6 months and the median OS was 27.2 months (37). These results suggest that it is possible to further optimize the dose and regimen of mAbs to combat BCBM.

Margetuximab (Margenza). Margetuximab (MGAH22; margetuximab-cmkb) (38) is a human/mouse chimeric and Fc-optimized mAb against HER2. Margetuximab and trastuzumab share the same HER2 receptor-binding epitope. However, margetuximab exhibits increased binding capacity to CD16A (FcγRIIIA) and decreased binding capacity to CD32B (FcγRIIB), thereby enhancing the activation of innate and adaptive immune responses whilst maintaining the antiproliferative effect of trastuzumab. In the SOPHIA (NCT02492711) (39) clinical trial, a total of 71 patients (71/536) had BM at baseline. Margetuximab improved the primary PFS over trastuzumab [HR, 0.76; 95% CI, 0.59-0.98; P=0.03; median, 5.8 (95% CI, 5.5-7.0) months vs. 4.9 (95% CI, 4.2-5.6) months], whilst demonstrating an acceptable safety profile, making it an alternative option for late-line therapy. However, the overall OS analysis did not reveal the superiority of margetuximab over trastuzumab, where its intracranial response rate requires further exploration.

3. Tyrosine kinase inhibitors (TKIs)

Compared with those of mAbs, the physical characteristics of small-molecule TKIs allow them to serve an important role

Table I. Mechanisms of action of anti-HER2 targeted drugs mentioned in the present review.

Type	Name	Mechanisms of action
Monoclonal antibodies	Trastuzumab	Binds to domain IV of HER2; inhibits downstream signalling and enables ADCC
	Pertuzumab	Binds to domain II of HER2, blocking downstream signalling and inhibiting heterodimerization
	Margetuximab	Fc engineered anti-HER2 antibody with an enhanced capacity for ADCC compared with trastuzumab
Tyrosine kinase inhibitors	Lapatinib	Binds to the ATP-binding intracellular domains of HER2 and HER1, thus inhibiting downstream signalling
	Pyrotinib	Binds to the ATP-binding intracellular domains of HER2, HER1 and HER4, thus inhibiting downstream signalling
	Neratinib	Binds to the ATP-bing intracellular domains of HER2, HER1 and HER4, thus inhibiting downstream signalling
	Tucatinib	Binds to the ATP-binding intracellular domains of HER2, thus inhibiting downstream signalling
Antibody-drug conjugates	T-DM1 T-DXd	Binds to domain IV of HER2, combine the activity of trastuzumab with targeted delivery of a cytotoxic payload
	ARX788	Binds to the HER2 receptor, releases a cytotoxic payload, AS269, thus inhibiting microtubule function.
	RC48	Binding to the HER2 extracellular domain, internalizing into the tumor cell, and releasing a cytotoxic payload (monomethyl auristatin E) to induce cell cycle arrest and apoptosis.
Bispecific antibodies	Zanidatamab	Binds to two distinct HER2 epitopes bispecifically, blocks the HER2 signaling pathway with an enhanced capacity for ADCC
	KN026	Binds to two different HER2 epitopes simultaneously, strongly inhibits the proliferation of HER2-overexpressing cancer cells.

HER, human epidermal growth factor receptor; ADCC, antibody-dependent cell-mediated cytotoxicity.

in crossing the BBB, thereby increasing drug concentrations in the brain (40). These findings suggest that TKIs may be a reasonable treatment strategy for CNS metastases (41,42). TKIs form a series of oral small-molecule drugs that promote apoptosis, inhibit the proliferation of cancer cells and act inside the cells (40). Because of its homologous structure, adenosine triphosphate (ATP) competitively binds to the intracellular ATP-binding domain of the epidermal growth factor receptor (EGFR) family, thereby inhibiting tyrosine kinase phosphorylation and subsequently blocking downstream signaling (43).

Lapatinib (Tykerb). Lapatinib is a first-generation TKI for the treatment of HER2-positive BC and is a tyrosine kinase inhibitor of both HER1 and HER2. In 2013, a single-arm phase II multicenter study (LANDSCAPE) (44) evaluated the efficacy of lapatinib plus capecitabine in patients with HER2-positive BC who had not previously received WBRT. The CNS-ORR was calculated to be 57.1%, where the median PFS was 5.5 months. BM is reduced by >80% in 67% of patients. In addition, in the NRG Oncology-KROG/RTOG 1119 (45) randomized trial, 143 patients were allocated to the following two groups: WBRT (37.5 Gy/3 weeks)/SRS (dose on the basis of lesion size) with or without lapatinib (1,000 mg per day for 6 weeks). The results reported that radiotherapy with lapatinib had a greater ORR (55 vs. 42%) at 4 weeks, suggesting that the combination may provide a short-term benefit. Therefore, the efficacy of lapatinib in the treatment of BM needs further clinical trial data for verification.

Pyrotinib (Irene). Pyrotinib is a small-molecule irreversible TKI that can target HER1, HER2 and HER4 (46). It was approved in China in 2018 in combination with capecitabine for the treatment of patients with advanced or metastatic BC (46). The PERMEATE trial (47) was designed to examine the efficacy of pyrotinib plus capecitabine in two separate cohorts of patients with HER2-positive BCBM. In cohort A (patients who had not previously received local radiotherapy), the intracranial ORR was 74.6% (median follow-up duration was 15.7 months). In cohort B (patients with active BM who progressed after radiotherapy), the intracranial ORR was 42.1% (median follow-up duration was 15.7 months). The latest follow-up data (48) (median follow-up, 40.5 months) revealed that cohort A had a median PFS of 10.7 months (95% CI, 7.6-14.9) and a median OS of 35.9 months (95% CI, 25.1-not reached). This previous study confirms the efficacy of the pyrotinib-capecitabine regimen for the treatment of HER2-positive BM.

In addition, the combination of pyrotinib, capecitabine and radiotherapy have also been assessed in another study

in patients with HER2-positive BC and BM. According to BROPTIMA (49), the 1-year CNS-PFS rate was 74.9% (95% CI, 61.9-90.7), the median CNS-PFS was 18.0 months (95% CI, 15.5-not reached) and the CNS-ORR was 85%, with 17 patients (42.5%) achieving complete response (CR) and partial response (PR). In addition to effectively controlling intracranial lesions, pyrotinib effectively reversed extracranial lesions, with an overall median PFS of 17.6 months (95% CI, 12.8-34.1). The safety of this combination was acceptable and it did not significantly impair central nervous system function.

Neratinib (Nerlynx). Neratinib is an oral irreversible TKI of HER1, HER2 and HER4 (50). The NEfERT-T study (51) compared neratinib with trastuzumab for the treatment of previously untreated HER2-positive metastatic BC (MBC), where the rates of symptomatic and progressive CNS recurrence were 8.3 and 17.3%, respectively (P=0.002). Although neratinib plus paclitaxel was not found to be superior to trastuzumab plus paclitaxel in terms of PFS for patients with HER2-positive MBC as a first-line treatment, it may delay the occurrence and decrease the incidence of CNS metastasis. In the randomized controlled phase III NALA trial (52), neratinib plus capecitabine was demonstrated to be superior to lapatinib plus capecitabine in terms of 1-year PFS (29 vs. 15%) for patients who received HER2-targeted therapies with two or more lines. In addition, neratinib provided superior control of CNS metastases (CNS-ORR, 26.3 vs. 15.4%) and can delay the occurrence of symptomatic BM requiring intervention (cumulative incidence, 22.8 vs. 29.2%). In the TBCRC022 Co3 phase II trial (53) investigating prior CNS-directed therapy and neratinib plus capecitabine in patients with BCBM, cohort A (who did not receive prior lapatinib) had a higher CNS-ORR rate compared with that in cohort B (who received prior lapatinib), with the CNS-ORR reported to be 49 vs. 33%. The median PFS was also different between the two cohorts (cohort A, 5.5 months; cohort B, 3.1 months). These findings suggest that neratinib exhibits a definite control effect on HER2-positive BM in patients treated with lapatinib.

Tucatinib (Tukysa). Tucatinib is an oral and reversible TKI that is highly selective for the HER2 domain (54). According to the HER2CLIMB study (55), the risk of intracranial progression was reduced by 68% (HR=0.32; 95% CI, 0.22-0.48; P<0.0001) in patients with HER2-positive BCBM. The median OS of the tucatinib group was 6.1 months longer compared with that of the control group (18.1 vs. 12.0 months). The CNS PFS was 9.9 months (95% CI, 8.4-11.7) in the tucatinib group, which was also superior to that observed in the control group (4.2 months; 95% CI, 3.6-5.7). According to follow-up (56) data (median follow-up of 26.9 months), the tucatinib combination group had greater clinical benefits in terms of CNS PFS and intracranial ORR. This subgroup analysis further supported the importance of tucatinib combination therapy for patients with HER2-positive brain metastases.

This trial also included a specialized subgroup of patients with untreated BM who used tucatinib plus trastuzumab and capecitabine in place of radiation therapy (66 patients). The median CNS-PFS in the tucatinib group was 8.1 months. Although the sample size was small, this analysis revealed that the combination of tucatinib with trastuzumab and capecitabine may provide an OS benefit for patients with untreated BM, possibly even delaying the duration of radiation therapy, which may cause cognitive impairments (11).

4. Antibody-drug conjugates (ADCs)

ADCs consist of mAbs, small-molecule drugs and linkers. The antibody binds to the target antigen on the surface of tumor cells. Through endocytosis and internalization, ADCs are transferred to lysosomes, where they release cytotoxic components and eventually lead to cell apoptosis (57).

Trastuzumab emtansine (T-DM1; Kadcyla). T-DM1 (58), which consists of trastuzumab and a cytotoxic component (the anti-microtubule drug DM1), exerts antitumor effects by inhibiting HER2 downstream signaling pathways, promoting ADCC, disrupting the microtubule network and causing apoptosis. Patients enrolled into the EMILIA study (59) were randomly allocated to the T-DM1 or lapatinib plus capecitabine groups. In addition, 45 and 50 patients had BM at baseline, respectively. In this subgroup, according to the RECIST 1.1 criteria (60), the median OS in the T-DM1 group was found to be 26.8 months, which was significantly superior compared with that in the lapatinib plus capecitabine group (12.9 months, HR=0.382; 95% CI, 0.18-0.80; P=0.0081).

The TH3RESA study (61) included patients with HER2-positive advanced BC who previously used trastuzumab and lapatinib. The subgroup analysis (RECIST V1.0) (62) revealed that T-DM1 treatment for patients with stable BM had a median OS of 17.3 months, which was superior compared with that of the investigator-selected treatment group (12.6 months, HR=0.62; 95% CI, 0.34-1.13), which was consistent with the beneficial trend noted in the overall population.

In another large-scale study, KAMILLA (63), among the 2,002 patients enrolled, 398 patients had BM at baseline. The median PFS was 5.5 months, whereas the median OS was 18.9 months (95% CI, 17.1-21.3). Among the 126 patients with measurable BM, the best overall response rate was 21.4%. Furthermore, 27 patients achieved stable disease (SD) for >6 months (assessed by RECIST V1.1). In total, 42.9% (54/126) patients had a >30% reduction in the sum of the maximum diameters of the target lesions. The clinical benefit rate was calculated to be as high as 42.9%. Therefore, notable antitumor activity was observed with T-DM1.

T-DXd (Enhertu). T-DXd (64) is comprised of a humanized mAb against HER2 linked to a DNA topoisomerase I inhibitor (Dxd) through a cleavable tetrapeptide linker. The amino acid sequence of the antibody partially overlaps with that of trastuzumab, but DXd is 10-fold more potent than SN-38, the active metabolite of irinotecan (65). Upon binding to HER2, T-DXd disrupts HER2 signaling and triggers ADCC (64). In addition, endocytosis-mediated cleavage of T-DXd inside cells releases DXd, which induces DNA damage and apoptosis (66).

DESTINY-Breast03 (67) was the first head-to-head clinical study of ADC agents designed to compare the therapeutic effect of T-DXd with that of the second-line standard treatment T-DM1. A total of 43 and 39 patients with stable BM were enrolled into the T-DXd and T-DM1 groups, respectively. The median PFS for patients with stable BM treated with

T-DXd was 15 months (95% CI, 12.5-22.2), which was significantly superior compared with that of patients with stable BM treated with T-DM1 (3 months, 95% CI=2.8-5.8). According to RECIST V1.1, the intracranial ORR of the T-DXd group was 63.9% (67), which was approximately twice as high as that of the T-DM1 group (33.4%). The intracranial CR rates of the T-DXd and T-DM groups were 27.8 and 2.8%, respectively, where that of the T-DXd group was ~10X higher compared with that of the T-DM1 group (68). One of the limitations was that the number of patients with stable BM was small, whereas patients with active BM were excluded from this trial.

The TUXEDO-1 trial (69) was initiated to fill the gap in data on the potential activity of T-Dxd in active BMs. The median PFS was 14 months, 13.3% (2/15) achieved CR, 60% (9/15) achieved PR and 20% (3/15) achieved SD. The best CNS-ORR was 73.3% (RANO-BM criteria) (70), which met the predefined primary study endpoint. The results indicated that T-Dxd not only exhibited clinically relevant activity in HER2-positive BC with active BM but also prolonged disease control despite the presence of BM. Therefore, these findings suggest that T-Dxd can be safely used to treat patients with HER2-positive BCBM to delay the initiation of local therapy. According to the latest final outcome analysis (71), the median follow-up was 26.5 months (95% CI, 23.5 months-not reached) and the median PFS was 21 months (95% CI, 13.3-not reached). The median OS was not reached (95% CI 22.2-not reached). Although TUXEDO-1 has several limitations, such as a single-center design and a small sample size, the long-term outcomes suggest that despite its large molecular size, T-DXd prolonged both intra- and extracranial disease control with acceptable tolerability whilst maintaining QoL function. The most frequent AEs were mild and moderate, such as fatigue (66.7%), nausea (46.7%) and anemia (46.6%).

Another multicenter retrospective real-world study, the ROSET-BM study (72), was performed to evaluate the efficacy of T-Dxd in patients with active BM and leptomeningeal carcinomatosis (LMC). The results from the total population revealed that the median PFS was 16.1 months, where the 1-year OS was 74.9%. Notably, among the 19 patients with LMC, the 1-year PFS and OS rates were 60.7 (95% CI, 34.5-79.1%) and 87.1% (95% CI, 57.3-96.6%), respectively. The results demonstrated sustained systemic and CNS disease control in patients with LMC.

Cohort 5 (patients with HER2-positive or HER2-low advanced or metastatic BC and untreated leptomeningeal carcinomatosis) of the DEBBRAH study (73) also showed positive activity in previously untreated HER2-positive patients with pathologically proven LMC, with no new safety concerns. Since the study remains at the initial stages, a longer follow-up will provide prospective data for this rare subgroup. In symptomatic patients, the sequence of systemic vs. local treatment may also have an impact on outcomes. The ongoing DESTINY-Breast12 study (74) (NCT04739761) will confirm the efficacy of T-DXd in patients with active BM in BCBM and will provide the greatest amount of information to date (n=250).

ADCs in developmental stages. Novel HER2-targeted ADCs, such as SYD985, ARX788 and RC48, are being explored. ARX788 (Anviti) (75) is a locus-specific ADC drug that was independently developed in China and has been applied in phase III clinical research in the field of BC (76). It introduces para-acetyl-phenylalanine (pAF) into the HER2 mAb and binds to the cytotoxic tubulin inhibitor amberstatin 269 (AS269) to form a stable oxime bond. This structure minimizes untargeted toxicity caused by the shedding of cytotoxic drugs during circulation and effectively reduces the total amount of drug required for therapy (77). Upon endocytosis into cells, ARX788 then releases pAF-AS269 into lysosomes, which induces cell death by binding to microtubules (79). This agent is currently being explored in patients with HER2-positive advanced BM (NCT05018702).

RC48 (adastuximab) (79), which is comprised of the HER2-targeted antibody disitamab loaded with the toxin monomethyl auristatin E (MMAE) and the valine-citrulline linker, has more potent antineoplastic activity compared with T-DM1. RC48-ADC showed consistent efficacy in both the HER2-positive subgroup and the HER2-low expression subgroup (NCT02881138 and NCT03052634) (80). In addition, 2.0 mg/kg Q2W had a more favorable benefit-risk ratio compared with the other doses (81). In addition, in trastuzumab- and lapatinib-resistant xenograft tumor models in nude mice (79), this novel ADC drug has also shown superior antitumor activity compared with that by T-DM1, suggesting its potential as an improved therapy for HER2-positive BC.

5. Bispecific antibodies (bsAbs)

Zanidatamab (Zani, Ziihera), also known as ZW25 (82), is a novel bispecific antibody that targets the extracellular II and IV domains of HER2. Its unique design yields multiple mechanisms of action, including dual HER2 signal blockade, increased clearance of HER2 proteins from the cell surface and enhanced antibody-dependent cytotoxic effects (83). In a previous phase I trial (NCT02892123) (84), Zani was well tolerated and showed preliminary antitumor activity in patients who had previously been treated with monotherapy or chemotherapy with advanced HER2-positive BC. The response rate of patients with BC (n=20) was 33% (median duration time, 5.1 months). A more recent phase Ib/2 trial (NCT04276493) (85), in which cohort A received 30 mg/kg Zani intravenously (IV) and cohort B received 1,800 mg Zani IV, both with docetaxel 75 mg/m2 IV Q3W. Preliminary results revealed that Zani combined with docetaxel had a manageable safety profile and an ORR of 90.9% (95% CI, 75.7-98.1; median follow-up time, 15.5 months) among the 33 patients evaluated for efficacy (EE), indicating promising antitumor activity in patients with advanced HER2-positive BC.

KN026 (Anbenitamab) (86) is a bsAb that binds to two different HER2 epitopes simultaneously, strongly inhibits the proliferation of HER2-overexpressing cancer cells and kills tumor cells that have developed resistance to the combination of trastuzumab and pertuzumab. According to the KN026-CHN-001 trial (87), 63 female patients with HER2-positive advanced BC who were previously treated with anti-HER2 targeted therapy (including trastuzumab plus pertuzumab, ADCs and TKI) were treated with IV KN026, with the dose increasing according to the '3 + 3 rule' (88). A

Table II. Clinical trials mentioned in the present review.

NCT identifier	Trial name	Official title
NCT00105456	registHER	An observational cohort study of patients with HER2 positive metastatic breast cancer
NCT00567190	CLEOPATRA	A Phase III, randomized, double-blind, placebo-controlled clinical trial to evaluate the efficacy and safety of pertuzumab + trastuzumab + docetaxel vs. placebo + trastuzumab + docetaxel in previously untreated HER2-positive metastatic breast cancer
NCT00967031	LANDSCAPE	A multi-center phase II clinical trial assessing the efficacy of the combination of lapatinib and capecitabine in patients with non-pretreated brain metastasis from HER2-positive breast cancer
NCT02536339	PATRICIA	An open-label, single-arm, phase II study of pertuzumab with high-dose trastuzumab for the treatment of central nervous system progression post-radiotherapy in patients with HER2-positive metastatic breast cancer
NCT02492711	SOPHIA	A phase III, randomized study of margetuximab plus chemotherapy vs. trastuzumab plus chemotherapy in the treatment of patients with HER2+ metastatic breast cancer who have received prior anti-HER2 therapies and require systemic treatment
NCT01622868	NRG Oncology-KROG/RTOG 1119	Phase II randomized study of whole brain radiotherapy/stereotactic radiosurgery in combination with concurrent lapatinib in patients with brain metastasis from HER2-positive breast cancer-a collaborative study of NRG Oncology and KROG
NCT03691051	PERMEATE	Pyrotinib plus capecitabine in patients with brain metastases from HER2-positive metastatic breast cancer: A single-arm, open-label, ahead study
NCT04582968	FDRT-BC010	A phase Ib/II pilot study of pyrotinib plus capecitabine combined with brain radiotherapy in HER2-positive breast cancer patients with brain metastases
NCT00915018	NEFERTT	A randomized, open-label, two-arm study of neratinib plus paclitaxel vs. trastuzumab plus paclitaxel as first-line treatment for ErbB-2-positive locally recurrent or metastatic breast cancer
NCT02624089	NALA trial	Evaluation of the effect of intraperitoneal nebulized ropivacaine on morphine consumption after laparoscopic appendectomy in children. A prospective, randomized double blind clinical trial
NCT00829166	EMILIA	A randomized, multi-center, phase III open-label study of the efficacy and safety of trastuzumab MCC-DM1 vs. capecitabine + lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior trastuzumab-based therapy
NCT01419197	TH3RESA	A phase III randomized, multi-center, two arm, open-label trial to evaluate the efficacy of trastuzumab emtansine compared with treatment of physician's choice in patients with HER2-positive metastatic breast cancer who have received at least two prior regimens of HER2-directed therapy
NCT01702571	KAMILLA	A two-cohort, open-label, multi-center study of trastuzumab emtansine (T-DM1) in patients with HER2-positive locally advanced or metastatic breast cancer who have received prior anti-HER2 and chemotherapy-based treatment
NCT03529110	DESTINY-Breast03	A phase III, multi-center, randomized, open-label, active-controlled study of DS-8201a (trastuzumab deruxtecan), an anti-HER2 ADC, vs. ado trastuzumab emtansine (T-DM1) for HER2-positive, unresectable and/or metastatic breast cancer subjects previously treated with trastuzumab and taxane
NCT04752059	TUXEDO-1	Phase II Study of trastuzumab-deruxtecan (DS-8201a) in HER2-positive breast cancer patients with newly diagnosed or progressing brain metastases
NCT04420598	DEBBRAH	Multi-center, open-label, single-arm, multicohort phase II clinical trial of trastuzumab deruxtecan (DS-8201a) in HER2+ advanced breast cancer with brain metastases and/or leptomeningeal carcinomatosis
NCT04739761	DESTINY-Breast12	An open-label, multinational, multicenter, phase IIIb/IV study of trastuzumab deruxtecan in patients with or without baseline brain metastasis with previously treated advanced/metastatic HER2-positive breast cancer
NCT05018702	ACE-Breast-06	A prospective, single-arm, single-center phase II clinical study of recombinant humanized anti-HER2 monoclonal antibody-AS269 conjugate (ARX788) in the treatment of HER2-positive breast cancer patients with brain metastases

Table II. Continued.

NCT identifier	Trial name	Official title
NCT02881138	C001 CANCER	A phase I study to evaluate the safety, tolerability and pharmacokinetics of RC48-ADC for injection in subjects with advanced malignant solid tumors with HER2-positivity
NCT03052634	C003 CANCER	A Phase Ib study to evaluate the efficacy, safety and pharmacokinetics of RC48-ADC for injection in subjects with advanced breast cancer with HER2-positive or HER2 low expression
NCT02892123	ZWI-ZW25-101	Phase I trial of ZW25 in patients with locally advanced (unresectable) and/or metastatic HER2-expressing cancers
NCT04276493	BGB-A317-ZW25-101	Phase Ib/II study investigating safety, tolerability, pharmacokinetics and preliminary antitumor activity of anti-HER2 bispecific antibody ZW25 in combination with chemotherapy with/without tislelizumab in patients with advanced HER2-positive breast cancer or gastric/gastroesophageal junction adenocarcinoma
NCT03619681	KN026-CHN-001	A single arm, open label, dose escalation phase I study to evaluate the tolerability, safety, pharmacokinetics and preliminary efficacy of KN026 monotherapy in patients with HER2-positive advanced malignant breast and gastric cancer
NCT01494662	TBCRC022	A Phase II trial of HKI-272 (Neratinib), neratinib and capecitabine and ado-trastuzumab emtansine for patients with HER2-positive breast cancer and brain metastases
NCT03975647	HER2CLIMB 02	Randomized, double-blind, phase III study of tucatinib or placebo in combination with ado-trastuzumab emtansine (T-DM1) for subjects with unresectable locally-advanced or metastatic HER2+ breast cancer (HER2CLIMB-02)
NCT04539938	HER2CLIMB-04	A single arm, open label phase II study of tucatinib in combination with trastuzumab deruxtecan in subjects with previously treated unresectable locally-advanced or metastatic HER2+ breast cancer
NCT02614794	HER2CLIMB	Phase II randomized, double-blinded, controlled study of tucatinib vs. placebo in combination with capecitabine and trastuzumab in patients with pre-treated unresectable locally advanced or metastatic HER2+ breast carcinoma
NCT05353361	SHR-A1811	A Phase Ib/II multi-center, open-label clinical trial of SHR-A1811 injection in combination with pyrotinib or pertuzumab or adebrelimab or paclitaxel for injection (albumin bound) in breast cancer
NCT04650451	BPX603-201A	A phase I/II, open-label, multi-center, non-randomized, safety and activity study of HER2-targeted dual switch CAR-T Cells (BPX-603) in subjects with previously treated advanced HER2-positive solid tumors
NCT03740256	H-43405 VISTA	A first in human phase I trial of binary oncolytic adenovirus in combination with HER2-specific autologous CAR-T cells in patients with advanced HER2 positive solid tumors
NCT03696030	NCI-2018-01270	A Phase I cellular immunotherapy study of intraventricularly administered autologous HER2-CAR T cells in patients with brain and/or leptomeningeal metastases from HER2-positive cancers

HER, human epidermal growth factor receptor; CAR-T, chimeric antigen receptor-T cells; ADC, antibody-drug conjugate; NRG Oncology, combination of National Surgical Adjuvant Breast and Bowel Project, Radiation Therapy Oncology Group and Gynecologic Oncology Group; KROG, Korean Radiation Oncology Group.

total of 23.8% (n=15) of the enrolled patients achieved a PR diagnosis. Additionally, CR was achieved in 1 patient (1.6%) and SD was achieved in 28 patients (44.4%). The confirmed ORR was 25.4% (95% CI, 15.3-37.9) and the disease control rate was 69.8% (95% CI, 57.0-80.8). The median PFS was 5.6 months.

Although there are no exact trial data on the application of ZANI and KN026 in patients with advanced BM, this novel class of drugs undoubtedly warrants further study.

6. Combination therapy

The majority of patients with advanced BM are treated with multiple lines of therapy and experience several problems, such as drug resistance, which greatly increases the difficulty of treatment (89). Combination therapy is particularly important. The combination and sequential treatment of multiple classes of drugs may provide improved therapeutic benefits.

Combinations of TKIs and ADCs. Although the use of ADCs can significantly improve the survival outcome of patients, the duration of tumor remission or benefit of ADC monotherapy remains limited because of the emergence of drug resistance mechanisms (90). Therefore, combination strategies with other antitumor drugs have become an important direction for drug development. In another cohort from the TBCRC022 study (91), the efficacy of neratinib plus T-DM1 was evaluated in patients with previously untreated BM (cohort 4A) and patients without prior T-DM1 therapy who progressed after local therapy (cohort 4B). Cohort 4C included patients who had received T-DM1 after local therapy progression. The CNS-ORRs in cohorts 4A, B and C were 33.3, 29.4 and 28.6%, respectively (median follow-up time: Cohort 4A, 33 months; cohort 4B, 28 months; cohort 4C, 28 months). In another randomized, double-blind, phase III study, HER2CLIMB02 (92), revealed the advantages of ADCs plus small-molecule tyrosine kinase inhibitors in HER2-positive advanced BC. The results indicated that in both patients previously treated with trastuzumab and taxane and patients with locally advanced/metastatic BC with a past history of BM, the median PFS of T-DM1 plus tucatinib was significantly longer compared with that of T-DM1 alone (9.5 vs. 7.4 months; HR=0.76). In addition, patients with BM (40% of all enrolled patients) also had a significant PFS benefit (median PFS, 7.8 vs. 5.7 months; HR=0.64), where no additional adverse events were observed in the combination group compared with T-DM1 alone. The combination of tucatinib plus T-DXd and tucatinib plus T-DM1 has been investigated in HER2CLIMB-04 (NCT04539938) (93) and CompassHER2 RD (NCT04457596) (94) patients, the data of which may provide novel opportunities for the treatment of patients with advanced BC and BM.

ADCs combined with immunotherapy. According to studies on the synergistic mechanism of HER2-targeted ADCs combined with immunotherapy, HER2-targeted therapy and immunotherapy involve complex crosstalk mechanisms. Anti-HER2 therapy promotes CD8+ T-cell infiltration into tumor tissue (95). The secretion of IFN-γ (96) by CD8+ T cells then enhances the anti-HER2-inhibiting effect on cell proliferation and upregulates programmed death-ligand 1 (PD-L1) expression. The HER2-targeted ADC SHR-A1811 (97) for injection can bind to and endocytose HER2-expressing tumor cells, cleave toxins through proteases in tumor cell lysosomes and induce cell cycle arrest and apoptosis. Adebrelimab (98) is a humanized anti-PD-L1 mAb that can specifically bind to PD-L1 molecules to block the programmed cell death protein 1/PD-L1 pathway, which leads to tumor immune tolerance and reactivates the antitumor activity of the immune system to achieve tumor treatment. Currently, clinical trials of adebrelimab combined with SHR-A1811 (NCT05353361) in BC have been approved.

7. Prospects and expectations

Protein degradation technology applied to targeted killing of the HER2 pathway. A novel targeted protein degradation system (99) has been recently designed based on phage-assisted continuous evolution technology. Degrons that can achieve targeted degradation, such as PROTAC, do not affect other non-target proteins and retain native genomic expression profiles (100), thereby minimizing interference with regulatory mechanisms that are critical to the natural biological functions of numerous proteins. In recent years, on the basis of the HER2-selective inhibitor tucatinib, a HER2 degrader was developed using PROTAC technology. The CH7C4 (101) compound was obtained by optimizing the linker, E3 ligase ligand and binding site. CH7C4 effectively inhibits HER2-driven cancer cell proliferation through durable HER2 degradation and strong inhibition of downstream pathways, where its antitumor activity was stronger compared with that of tucatinib both *in vitro* and *in vivo* (101). This technology provides novel ideas for the development of new drugs for the treatment of HER2-positive BC.

Chimeric antigen receptor T-cell (CAR-T cell) immunotherapy exhibits numerous possibilities. CAR-T (102) cells are generated from T cells isolated from patients' peripheral blood and engineered *in vitro* to express synthetic receptors that recognize tumor antigens. CAR-T cells are subsequently cultured for expansion and infused back into patients (103). In the past, this type of immunotherapy was mainly used for treating hematologic tumors. Several clinical trials in different solid tumors are underway around the world (104), including for BC (NCT04650451, NCT03740256 and NCT03696030). Experimental data (105) have demonstrated that trastuzumab-resistant tumors can be effectively eliminated by HER2-CAR-T cells, indicating that the clinical use of trastuzumab-derived HER2-specific CAR-T cells represent an option for the treatment of trastuzumab-resistant tumors. In addition, other experimental data (106) have demonstrated that HER2-CAR-T cells containing the 4-1BB costimulatory domain exhibit superior tumor targeting ability, reducing the T-cell exhaustion phenotype and enhancing the proliferative capacity compared with those containing the CD28 costimulatory domain. Local intracranial delivery of HER2-CARs has shown potent antitumor activity in orthotopic xenograft models and in regional intraventricular delivery (106,107), which is undoubtedly worthy of further research.

8. Conclusion

On the basis of the current research progress in the treatment of BCBM, the overall efficacy of single macromolecular mAbs is not satisfactory, since they mainly serve a role in the extracranial control of this disease. Small molecule TKIs have demonstrated significant clinical benefits for patients with active BM, whereas ADC drugs have shown encouraging therapeutic activity and clinical benefit in both patients with BM and LMC. In summary, tucatinib and T-DXd are currently the two most promising therapeutic drugs in the field of BCBM. The direction of the next stage of development may target improving combination therapy. The application of Trop-2 targeted ADCs in the treatment of BCBM should be explored. With the continuous influx of research data, the rational deployment of drugs for HER2-positive BCBM will prolong PFS and improve the quality of life of patients (Table II).

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Authors' contributions

ZYW conducted literature searches, evaluated all relevant literature and wrote the first draft of the manuscript. HMH conceived the topic area, supervised the search strategy and writing, and reviewed and revised the manuscript drafts. All the authors read and approved the final manuscript.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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