Systemic Management of Brain Metastases in HER2+ Breast Cancer in 2022

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Abstract: Up to half of all patients with metastatic human epidermal growth factor receptor 2–positive (HER2+) breast cancer will eventually acquire brain metastases (BrMs), which are associated with reduced overall survival and decreased quality of life. Although the median overall survival was previously less than a year, novel systemic treatments have significantly extended life expectancy in patients with HER2+ breast cancer BrMs. The current first-line standard of care for all patients with HER2+ metastatic breast cancer, regardless of BrMs status, is dual HER2 antibody therapy with pertuzumab/trastuzumab plus a taxane. Second-line systemic therapy has recently evolved, with the option of trastuzumab deruxtecan (T-DXd) or tucatinib in combination with trastuzumab and capecitabine. T-DXd has shown dramatically superior progression-free survival in comparison with trastuzumab emtansine (T-DM1) in patients with stable BrMs in the second-line setting. Patients who have untreated or locally treated/progressive BrMs may benefit from a regimen with robust intracranial response rates, such as tucatinib in combination with trastuzumab and capecitabine. Third-line therapy and beyond includes multiple options that require careful selection, with the patient's BrMs status, comorbidities, and performance status taken into account. In this review, we focus on current management and evolving strategies for the treatment of patients with HER2+ breast cancer BrMs.

Background

Breast cancer (BC) is the most frequently diagnosed cancer globally and the leading cause of cancer-related death in women.[1] In 2021, an estimated 284,200 new cases of invasive BC were diagnosed among women in the United States.[2] Human epidermal growth factor receptor 2–positive (HER2+) BC is a common subtype, occurring in

approximately 15% to 20% of women with BC.[3] Major advances in the treatment of early-stage HER2+ BC, including the addition of novel HER2-targeted agents such as trastuzumab, pertuzumab (Perjeta, Genentech), trastuzumab emtansine (T-DM1; Kadcyla, Genentech), and neratinib (Nerlynx, Puma) to systemic chemotherapy, have dramatically improved outcomes. Despite treatment with the most up-to-date regimens, including neoadjuvant trastuzumab and pertuzumab plus chemotherapy followed by T-DM1, in patients with residual disease, brain metastases (BrMs) as the first site of recurrence still develop in 6% of patients who have received T-DM1.[4] Strikingly, BrMs occur in up to 50% of patients with metastatic HER2+ BC during the course of their disease.[5-8] The median time to the onset of HER2+ BrMs is 13.3 months following a diagnosis of metastatic disease.[6] BrMs most often develop during first- or second-line therapy, whereas extracranial disease is often stable.[9] Initial local treatment options include surgical resection for solitary BrMs or for space-occupying lesions that are causing symptoms. Radiotherapy is the standard-of-care local therapy for BrMs and can include whole-brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS).[10]

HER2+ BrMs remain incurable, and the overall survival (OS) of patients with these lesions is 30 months after diagnosis.[11] However, the systemic treatment of HER2+ BC BrMs has substantially improved in recent years owing to the availability of multiple novel HER2-directed regimens, including tyrosine kinase inhibitors (TKIs) and antibody-drug conjugates (ADCs), with intracranial activity. Challenges to the development of effective systemic therapies with intracranial activity include the difficulty of penetrating the blood-brain barrier (BBB), the presence of efflux transporters, the exclusion of patients from clinical trials, and discordant intracranial/extracranial responses to treatment.[12,13] Nonetheless, we have made substantial progress in the systemic treatment of patients with HER2+ BC BrMs, and the US Food and Drug Administration (FDA) has granted the first approval of a therapy with a specific indication and activity in patients with HER2+ BrMs. This article reviews the most recent advances in systemic therapies for patients with HER2+ BC BrMs.

Local Therapy for Brain Metastases in HER2+ Breast Cancer

BrMs can significantly affect quality of life; therefore, rapid and effective multidisciplinary management involving neurosurgery, radiation oncology, medical oncology, and palliative care is essential. Local therapies such as surgical resection, radiation therapy with focused SRS, and WBRT are all options.[14] The choice of management depends on multiple factors, including number and location of lesions, presence of neurologic symptoms, performance status, and extracranial disease status. For patients with a single large BrM, good performance status, and relatively stable extracranial disease, surgical resection followed by radiation therapy to the resected tumor bed offers a survival benefit.[15-17] SRS is preferable for patients with multiple lesions that are limited in number; the upper limit of the number of lesions that can be treated varies greatly among treatment centers owing to differences in the use of newer techniques.[18] Research is ongoing to determine whether patients with a large number of lesions do better with SRS or WBRT (NCT03550391).

WBRT is recommended for patients with multiple lesions and widespread brain involvement, although the adverse effects on neurocognitive functioning and quality of life can be significant.[19,20] New approaches to WBRT are now available, including hippocampal avoidance (HA-WBRT) and the addition of neuroprotectants such as memantine.[21-23] An alternative to SRS or WBRT is a trial of a highly brain-penetrable regimen, such as tucatinib (Tukysa, Seagen) plus trastuzumab and capecitabine. The HER2CLIMB trial, which analyzed this regimen, included patients with untreated BrMs in addition to patients with treated/stable and treated/progressive BrMs.[24] This strategy requires multidisciplinary oversight and patient counseling regarding risks and possible benefits. Short-interval magnetic resonance imaging (MRI) of the brain (ie, every 6-9 weeks) is crucial for close monitoring.

Systemic Therapy for Brain Metastases in HER2+ Breast Cancer

HER2-targeted therapy should be initiated or continued following local intracranial therapy because studies have shown that HER2 therapy markedly improves OS in patients with HER2+ BC BrMs.[25,26] Current clinical practice guidelines from the American Society of Clinical Oncology (ASCO) recommend continuing current systemic treatment at the time of first central nervous system (CNS) progression if extracranial disease is stable after local therapy.[10] It is also recommended that patients whose systemic disease is progressive at the time of first intracranial progression be transitioned to the next line of therapy. For those with second brain progression and stable extracranial disease, it is recommended that transition to a therapy that optimizes intracranial response and progression-free survival (PFS) be considered. Given the availability of newer HER2-directed therapies that specifically improve OS in patients with HER2+ BC BrMs, secondary prevention strategies aimed at prolonging intracranial PFS and OS are now being evaluated prospectively.

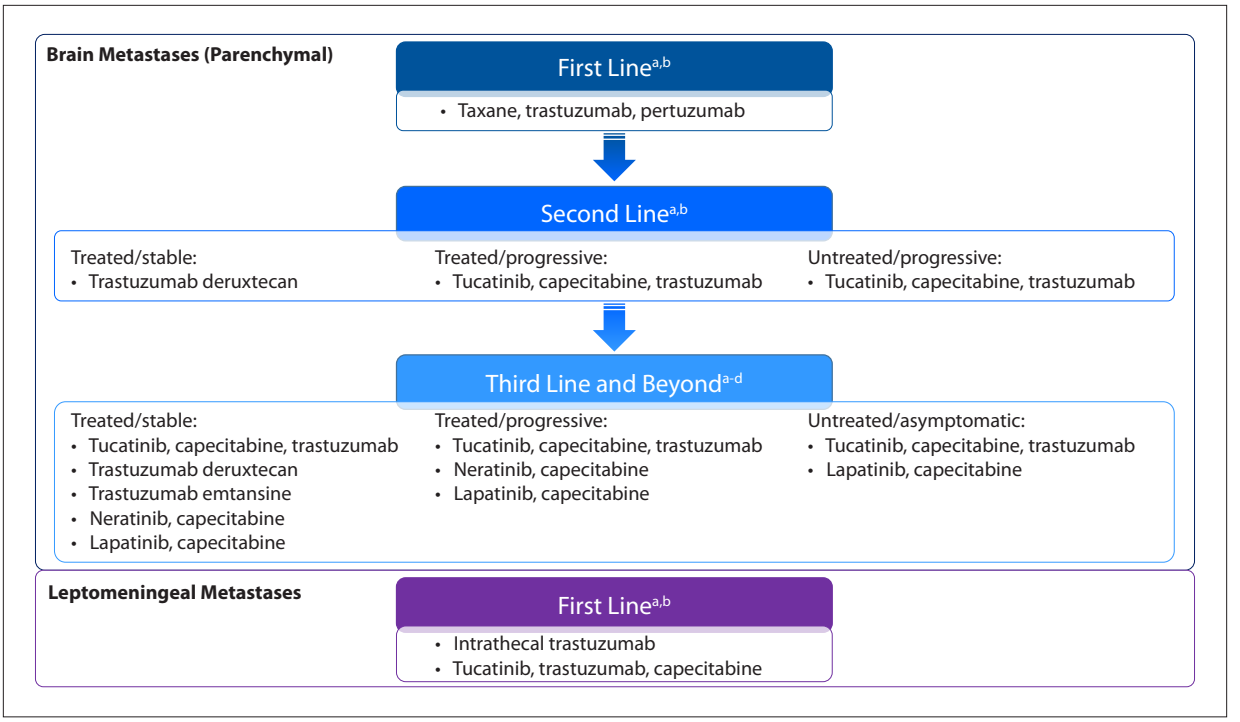

Figure. Recommended sequencing of systemic therapies for breast cancer brain metastases and leptomeningeal metastases.

[a]Encourage clinical trial participation.

[b]Patients with stable systemic/extracranial disease at the time of first intracranial progression can continue the same systemic treatment after any required local therapy until further progression.

[c]Efficacy of trastuzumab emtansine after trastuzumab deruxtecan is unknown.

[d]Efficacy of neratinib and lapatinib after tucatinib is unknown.

First-Line Treatment

Trastuzumab, Pertuzumab, and a Taxane. Trastuzumab, the first HER2-targeting monoclonal antibody, revolutionized the treatment of HER2+ BC. Although a concern has been that trastuzumab appears to be too large to cross the BBB, a recent positron emission tomography study using ^{89}Zr-trastuzumab in patients with HER2+ metastatic BC showed that trastuzumab can, in fact, access BrMs, possibly because of a compromised blood-brain/blood-tumor barrier.[27] Retrospective studies have indicated that trastuzumab is associated with an increased time to the development of BrMs and improved survival after the development of BrMs.[26,28]

The current standard-of-care first-line treatment for patients with HER2+ metastatic BC is trastuzumab plus pertuzumab and a taxane (Figure), on the basis of results of the landmark CLEOPATRA clinical trial (Table).[10,29] This regimen is recommended regardless of BrMs status. Like trastuzumab, pertuzumab is an anti-HER2 monoclonal antibody, but it binds HER2 at a different epitope of the HER2 extracellular domain (subdomain 2). Pertuzumab also blocks HER2/HER3 dimer formation and subsequent downstream signaling cascades.[30] CLEOPATRA was a randomized, multicenter, international phase 3 clinical trial that evaluated the addition of pertuzumab (vs placebo) to trastuzumab and docetaxel in patients with de novo metastatic HER2+ BC or patients presenting at least 12 months after the completion of adjuvant HER2-directed therapy. Either pertuzumab or placebo was given with trastuzumab until disease progression; docetaxel was given for 6 cycles or longer at the investigators' discretion. The final analysis showed significantly improved median PFS of 18.7 months (HR, 0.69; 95% CI, 17-22) and OS of 57.1 months (HR, 0.69; 95% CI, 0.58-0.82) with pertuzumab vs median PFS of 12.4 months and OS of 40.8 months with placebo, establishing this regimen as first-line treatment in metastatic HER2+ disease.[31,32] Of note, patients were excluded if they had CNS metastases, although an exploratory analysis of the incidence and time to development of BrMs was performed. Although the incidence of BrMs as the first site of disease progression was similar in the 2 arms (13.7% in the pertuzumab

Table. Key Trials in HER2+ Breast Cancer Brain Metastases

Trial Name, Identifier (Phase)	Intervention(s)	BrMs Eligibility	Drug Class(es)	Overall PFS/OS/ORR	PFS/OS/ORR in BrMs Cohort
PATRICIA, NCT02448420 (2)	High-dose trast + pert	Progressive BrMs, >3 wk since radiation	mAbs (HER2)	PFS: N/A OS: N/A ORR: N/A	PFS: N/A OS: N/A ORR: N/A iPFS: N/A iORR: 11% (high-dose trast with pert)[67]
CLEOPATRA,[a] NCT00567190 (3)	Pert + trast + taxel vs Placebo + trast + taxel	Excluded BrMs	mAbs (HER2) + chemo vs mAb (HER2) + chemo	PFS: 18.7 mo (pert arm) vs 12.4 mo (placebo arm)[31,32] OS: 57.1 mo (pert arm) vs 40.8 mo (placebo arm)[31,32] ORR: N/A	PFS: N/A OS: 34.4 mo (pert arm) vs 26.3 mo (placebo arm)[33] ORR: N/A Time to first CNS metastases: 15.0 mo (pert arm) vs 11.9 mo (placebo arm)[33] iORR: N/A
DESTINY-Breast01, NCT03248492 (1b/2)	T-DXd	Treated, asymptomatic BrMs	ADC	PFS: 19.4 mo[37] OS: not reached[36] ORR: 60.9%[36]	PFS: 18.1 mo[36,38] OS: N/A ORR: 58.3%[38] iPFS: N/A iORR: N/A
DESTINY-Breast03, NCT03529110 (3)	T-DXd vs T-DM1	Inactive BrMs, >2 wk since radiation	ADC vs ADC	PFS (BICR): not reached (T-DXd arm) vs 6.8 mo (T-DM1 arm)[39] OS: N/A[39] ORR (BICR): 79.1% (T-DXd arm) vs 34.2% (T-DM1 arm)[39]	PFS: N/A OS: N/A ORR: N/A iPFS: N/A iORR: N/A
HER2CLIMB, NCT02614794 (2)	Tucatinib[b] + cape + trast vs Placebo + cape + trast	Untreated, treated/stable, or treated/progressive BrMs	TKI (rev) + chemo + mAb (HER2) vs mAb (HER2) + chemo	PFS: 7.8 mo (tucatinib arm) vs 5.6 mo (placebo arm)[24] OS: 21.9 mo (tucatinib arm) vs 17.4 mo (placebo arm)[24] ORR: 40.6% (tucatinib arm) vs 22.8% (placebo arm)[24]	PFS: 7.6 mo (tucatinib arm) vs 5.4 mo (placebo arm)[24] OS: 18.1 mo vs 12 mo (placebo/cape/trast)[47]; 20.7 mo (tucatinib arm) vs 11.6 mo (placebo arm) in active BrMs[47]; 16.5 mo (tucatinib arm) vs 11.2 mo (placebo arm) in previously untreated BrMs[47]; 15.7 mo (tucatinib arm) vs 13.6 mo (placebo arm) in stable BrMs[47] ORR: N/A iPFS: 9.9 mo (tucatinib arm) vs 4.2 mo (placebo arm)[47]; 9.5 mo (tucatinib arm) vs 4.1 mo (placebo arm) in active BrMs[47]; 8.1 mo (tucatinib arm) vs 3.1 mo (placebo arm) in previously untreated BrMs[47]; 13.9 mo (tucatinib) vs 5.6 mo (placebo) in stable BrMs[47] iORR: 47.3% (tucatinib arm) vs 20.0% (placebo arm) in active BrMs[47]; 47.1% (tucatinib arm) vs 16.7% (placebo arm) in previously untreated BrMs[47]

Table. *(Continued)* Key Trials in HER2+ Breast Cancer Brain Metastases

Trial Name, Identifier (Phase)	Intervention(s)	BrMs Eligibility	Drug Class(es)	Overall PFS/OS/ORR	PFS/OS/ORR in BrMs Cohort
EMILIA, NCT00829166 (3)	T-DM1 vs XL	Treated, asymptomatic BrMs, >2 mo since radiation	ADC vs TKI (rev) + chemo	PFS: 9.6 mo (T-DM1 arm) vs 6.4 mo (XL arm)[53,54] OS: 29.9 mo (T-DM1 arm) vs 25.9 mo (XL arm)[53] ORR: 43.6%[52]	PFS: 5.9 mo vs 5.7 mo (cape/lap)[54] OS: 26.8 mo vs 12.9 mo (cape/lap)[54] ORR: N/A iPFS: N/A iORR: N/A
KAMILLA, NCT01702571 (3b)	T-DM1	Asymptomatic BrMs, >2 wk since radiation	ADC	PFS: 6.9 mo[81] OS: 27.2 mo[81] ORR: N/A	PFS: 5.5 mo[56] OS: 18.9 mo[56] ORR: 21.4%[56] iPFS: N/A iORR[d]: 42.9%5[6]; 50.0% vs 32.7% vs 49.3% (WBRT <30 d prior vs WBRT ≥30 d prior vs no WBRT prior)[56]
LANDSCAPE,[c] NCT00967031 (2)	XL	BrMs not previously treated with WBRT, cape, or lap	TKI (rev) + chemo	PFS: N/A OS: N/A ORR: N/A	PFS: 5.5 mo[59] OS: 17.0 mo[59] ORR: N/A iPFS: 5.5 mo[59] iORR: 65.9% (untreated)[59]
NALA, NCT01808573 (3)	Neratinib + capecitabine vs XL	Stable, asymptomatic BrMs	TKI (irrev) + chemo vs TKI (rev) + chemo	PFS: 8.8 mo (neratinib arm) vs 6.6 mo (lap arm)[61] OS: 24.0 mo (neratinib arm) vs 22.2 mo (lap arm) (difference not statistically significant)[61] ORR: 32.8% (neratinib arm) vs 26.7% (lap arm)[61]	PFS: N/A OS: N/A ORR: N/A iPFS: N/A iORR: N/A Cumulative incidence of intervention for BrMs: 22.8% (neratinib arm) vs 29.2% (lap arm)[61]
TBCRC-022,[c] NCT01494662 (2)	Neratinib + capecitabine	Progressive BrMs (cohort 3); lap-naive (cohort 3A), or lap-exposed (cohort 3B)	TKI (irrev) + chemo	PFS: N/A OS: N/A ORR: N/A	PFS: 5.5 mo (lap-naive); 3.1 mo (lap-exposed)[82] OS: 13.3 (lap-naive) mo; 15.1 mo (lap-exposed)[82] ORR: 14% (lap-naive, extracranial ORR); 43% (lap-exposed, extracranial ORR)[82] iPFS: N/A iORR: 49% (lap-naive), 33% (lap-treated; treated/progressive with cape/neratinib)[82]

[a]CLEOPATRA excluded patients with BrMs at enrollment but monitored for development of BrMs as first site of disease progression. Outcomes from patients with development of BrMs on study are reported.

[b]FDA-approved for BC BrMs.

[c]LANDSCAPE and TBCRC-022 required patients to have BrMs for eligibility; therefore, for consistency, the PFS/OS/ORR values from this study are reported as in the BrMs cohort (last column).

[d]Reduction of ≥30% in sum of major diameters of previously untreated BC BrMs.

ADC, antibody-drug conjugate; BC, breast cancer; BICR, blinded independent central review; BrMs, brain metastases; cape, capecitabine; CNS, central nervous system; d, day(s); HER2, human epidermal growth factor receptor 2; iORR, intracranial overall response rate; iOS, intracranial overall survival; iPFS, intracranial progression-free survival; irrev, irreversible; lap, lapatinib; mAb, monoclonal antibody; mo, months; N/A, not available; pert, pertuzumab; rev, reversible; taxel, docetaxel; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor (see review[83]);mo, month(s); trast, trastuzumab; WBRT, whole-brain radiation therapy; wk, week(s); XL, capecitabine + lapatinib.

arm vs 12.6% in the placebo arm), the median time to the development of BrMs as the first site of disease progression was significantly longer in the pertuzumab arm than in the placebo arm: 15.0 months vs 11.9 months, respectively.[33] OS in the patients with BrMs as the first site of disease progression also showed a trend in favor of pertuzumab, trastuzumab, and docetaxel (hazard ratio [HR], 0.66), with a median OS of 34.4 months in the pertuzumab arm and 26.3 months in the placebo arm.

Thus, at present, although the landscape of systemic treatments for HER2+ metastatic BC is rapidly changing, first-line systemic therapy for patients with HER2+ BrMs remains a taxane plus trastuzumab and pertuzumab. Generally, we offer this regimen as first-line therapy in conjunction with adequate local therapy to BrMs in patients who have either de novo HER2+ BC or metastatic disease presenting 12 months or more following adjuvant therapy.

Second-Line Therapy

T-DXd: Standard Second-Line Therapy for Patients With Stable BrMs. Trastuzumab deruxtecan (T-DXd) is an ADC that is composed of a humanized monoclonal antibody mirroring trastuzumab, a cleavable tetrapeptide-based linker, and a potent topoisomerase I inhibitor as the cytotoxic drug payload. The drug-to-antibody ratio of T-DXd is higher than that in another approved ADC, T-DM1, with a tubulin destabilizer payload of approximately 8 for T-DXd vs 3 to 4 for T-DM1.[34] Unlike that of T-DM1, the released payload of T-DXd easily crosses the cell membrane, potentially having a potent cytotoxic effect on neighboring tumor cells regardless of target expression and possibly overcoming tumor heterogeneity.[35] In addition, the released payload has a short half-life, which is designed to minimize systemic exposure.[36]

The single-arm phase 1b/2 DESTINY-Breast01 trial was the first to evaluate T-DXd in adults with HER2+ metastatic BC previously treated with T-DM1 (Table).[36] Patients were excluded if they had untreated or symptomatic BrMs. A total of 184 patients were included, with a median of 6 previous treatment lines. A robust 60.9% overall response rate (ORR) was noted, and the median PFS was 19.4 months.[37] On the basis of these findings, the FDA approved T-DXd in December 2019 for the treatment of patients with HER2+ metastatic BC after 2 or more anti-HER2–based regimens. In addition, a subgroup analysis of the DESTINY-Breast01 trial was performed on the 24 enrolled patients with treated and asymptomatic BrMs.[38] The ORR was 58.3%, median PFS was 18.1 months, and the median duration of response was 16.9 months. Among the 14 patients with baseline diameters of BrMs, the CNS response rate per the investigators was 50% (7 of 14 patients).

T-DM1 was widely regarded as the standard-of-care second-line therapy for HER2+ metastatic BC during the last decade until the recent practice-changing results of the DESTINY-Breast03 clinical trial were published. DESTINY-Breast03 was a randomized, international phase 3 study comparing T-DXd vs T-DM1 in patients with metastatic HER2+ BC previously treated with trastuzumab and a taxane in the advanced setting. Patients were stratified by hormone receptor status, prior pertuzumab treatment, and visceral disease status and then randomly assigned to T-DXd at a dose of 5.4 mg/kg every 3 weeks or to T-DM1 at a dose of 3.6 mg/kg every 3 weeks. This groundbreaking study revealed a stunning PFS advantage for T-DXd by blind independent central review, with an HR of 0.2840 (P=7.8 × 10^{-22}); median PFS was not reached for the T-DXd arm vs 6.8 months for the T-DM1 arm.[39] By investigator assessment, median PFS was 25.1 months for T-DXd vs 7.2 months for T-DM1 (HR, 0.26; P=6.5 × 10^{-24}). The estimated 12-month OS event rates were 94.1% for T-DXd and 85.9% for T-DM1 (HR, 0.5546). Importantly, no grade 4 or 5 interstitial lung disease was reported in the trial, which was reassuring given that several grade 5 deaths had occurred in earlier-phase trials.

Patients with stable BrMs were eligible for the DESTINY-Breast03 trial and made up 15% of the trial population. Patients were excluded if they had symptomatic BrMs or had received WBRT within 2 weeks of study enrollment. Subgroup analysis of PFS confirmed a benefit of T-DXd vs T-DM1 in the patients who had stable BrMs, with an HR of 0.3796 (95% CI, 0.2267-0.6357).[39] In a recent updated analysis presented at the 2021 San Antonio Breast Cancer Symposium (SABCS), median PFS in the patients with BrMs was 15 months in the T-DXd treatment arm compared with 3 months in the standard treatment arm. Of 36 patients who had BrMs treated with T-DXd, 23 (63.9%) had a response in the brain; 10 of these patients had a complete response.[40] In contrast, of the 36 patients who had BrMs treated with T-DM1, 12 (33.3%) had an intracranial response and 1 had a complete response. This study is practice-changing, and the results have led to a paradigm shift in the second-line treatment of HER2+ metastatic BC with and without stable BrMs.

Similarly, data from the TUXEDO-1 trial investigating T-DXd in patients with HER2+ BC and active BrMs, presented at the 2021 European Society for Medical Oncology (ESMO) Congress, showed that at a median follow-up of 3.5 months, 9 patients were still on treatment.[41] A total of 60% had received prior radiotherapy for BrMs, and 70% had received prior T-DM1. T-DXd yielded an intracranial response in 5 of 6 patients (83.3%) enrolled in the first stage, including 3 of 4 patients who had progressing disease after prior local therapy.[41] DEBBRAH is a phase 2 trial assessing T-DXd in patients with

BrMs of various stages and/or leptomeningeal metastasis. Preliminary results recently presented at SABCS 2021 showed efficacy in both stable and progressing HER2+ BC BrMs after local treatment, with manageable toxicity.[42] Of 9 patients with progressive BC BrMs, 4 (44.4%) had a partial response and another 4 had a best response of stable disease, only one of which was longer than 24 weeks.[42] Of 8 patients with stable BC BrMs at enrollment, 7 (87.5%) were alive without disease progression at 16 weeks.

Given that the patients with stable BrMs derived substantial benefit, T-DXd should be a standard-of-care second-line therapy for this population (Figure). The global phase 3b/4 DESTINY-Breast12 clinical trial (NCT04739761; see eTable) will offer more information on the activity of T-DXd in untreated or treated/progressive BrMs, with results anticipated in 2024. T-DXd should not be considered for patients with previous or underlying interstitial lung disease, given the known risk for interstitial lung disease associated with T-DXd treatment per the experience in DESTINY-Breast01 and DESTINY-Breast03.

Tucatinib, Trastuzumab, and Capecitabine. HER2-targeted TKIs have emerged as a promising drug class for BrMs because of their small molecular size and ability to cross the BBB.[43-45] Tucatinib is a novel TKI that is highly selective for the kinase domain of HER2, sparing other HER family members and thus improving the toxicity profile.[46] The HER2CLIMB clinical trial was a randomized, double-blind, placebo-controlled study comparing tucatinib vs placebo in combination with trastuzumab and capecitabine in patients with HER2+ metastatic BC previously treated with trastuzumab, pertuzumab, and T-DM1.[24] A unique aspect of the trial was that it enrolled a large proportion (48%) of patients with BrMs, including previously untreated, treated/stable, and treated/progressive BrMs. Notably, at the time HER2CLIMB was designed, no systemic treatments for patients with BC and active BrMs had been approved.

HER2CLIMB demonstrated clinically meaningful and statistically significant improvements in OS, PFS, and confirmed ORR in all patients treated with tucatinib, trastuzumab, and capecitabine.[24] The study reported a median PFS of 7.8 months with tucatinib vs 5.6 months with placebo. Median OS was 21.9 months with the addition of tucatinib vs 17.4 months with placebo.

Among the patients with BrMs, the PFS rate at 1 year was 24.9% in the tucatinib group and 0% in the placebo group (HR, 0.48), and the median PFS was 7.6 months in the tucatinib group and 5.4 months in the placebo group. Of note, patients with isolated intracranial progression were allowed to undergo radiation and then continue in the study. A further exploratory analysis of the population with BrMs showed that the addition of tucatinib to trastuzumab and capecitabine doubled the intracranial ORR, reduced the risk for intracranial progression or death by two-thirds, and reduced risk for death by nearly half.[47] Among the 291 patients with BrMs, the estimated 1-year intracranial PFS (iPFS, or CNS-PFS) rate was 40.2% in the tucatinib arm and 0% in the control arm. The risk for progression in the brain or death was reduced by 68% in the tucatinib arm vs the control arm (HR, 0.32; 95% CI, 0.22-0.48; P<.0001). The median iPFS was 9.9 months in the tucatinib arm and 4.2 months in the control arm. The estimated 1-year OS rate was 70.1% in the tucatinib arm and 46.7% in the control arm. The risk for death was reduced by 42% in the tucatinib arm vs the control arm (HR, 0.58; 95% CI, 0.40-0.85; P=.005).[47] Of these 291 patients, 66 with untreated BrMs who elected to enter HER2CLIMB in lieu of radiation therapy had a median iPFS of 8.1 months, suggesting a possible opportunity for delaying radiation therapy in highly selected cases.[47]

On the basis of these results, the FDA approved tucatinib in April 2020 for use in combination with trastuzumab and capecitabine in patients with or without BrMs previously treated with 1 or more prior anti-HER2–based regimens in the metastatic setting. Importantly, HER2CLIMB was the first randomized trial to demonstrate statistically significant and clinically meaningful improvements in PFS and OS among patients with BrMs, including those with untreated or treated/progressive BrMs.

We consider tucatinib, trastuzumab, and capecitabine in the second-line setting for patients with untreated or treated/progressive BrMs when an intracranial response is needed. Examples could include patients whose BrMs have undergone SRS or WBRT yet continue to progress intracranially, or patients trying to avoid WBRT and managed under careful multidisciplinary monitoring. The activity of tucatinib, trastuzumab, and capecitabine following progression on T-DXd is unknown, although activity following trastuzumab/pertuzumab and T-DM1 is well established.

Third-Line Therapy and Beyond

Further research is needed to understand the optimal sequence and, ultimately, the efficacy of HER2-targeted therapies after disease progression on T-DXd in patients with HER2+ metastatic BC BrMs. Several options are currently available, including ADCs, TKIs, and chemotherapy regimens with trastuzumab (Figure). These regimens are known to be effective after disease progression on trastuzumab; however, none of them has been studied after disease progression on T-DXd. Tucatinib given with trastuzumab/capecitabine is our first-choice TKI for HER2+ BrMs, given the PFS and OS benefit in treated/stable, untreated, and treated/progressive HER2+ BrMs. This regimen is our recommendation in the third line for

HER2+ BC BrMs if T-DXd has been given in the second line. The choice and sequence of therapies beyond trastuzumab/pertuzumab, T-DXd, and tucatinib/trastuzumab/capecitabine generally depend on patient and physician preference, with differences in side effect profiles kept in mind. It is always reasonable to consider a non-brain/extracranial biopsy after progression on second- or third-line therapy to verify continued HER2 overexpression or amplification. It is important to note, however, that even if extracranial disease has lost HER2 overexpression, concurrent BrMs could still be HER2-driven. Divergent subtypes among systemic disease and BrMs are noted in up to 36.3% of cases, and in 10.4% of HER2+ cases.[48,49]

Trastuzumab Emtansine. T-DM1 is an ADC in which the cytotoxic agent DM1 (anti-microtubule) is conjugated to trastuzumab via a stable linker, facilitating the intracellular delivery of DM1 to HER2-overexpressing tumor cells and resulting in the inhibition of microtubule function and cell death.[50] Like trastuzumab, T-DM1 inhibits HER2 signaling, prevents HER2 shedding, and induces antibody-dependent cellular cytotoxicity.[51] Second-line treatment consisting of T-DM1 was the standard of care for nearly a decade, until recently. The EMILIA trial was a phase 3 study of T-DM1 vs capecitabine/lapatinib (XL) in patients with HER2+ metastatic BC previously treated with trastuzumab and a taxane.[52] Patients were ineligible if they had symptomatic BrMs or had been treated for these metastases within 2 months before randomization. Median OS was 29.9 months (95% CI, 26.32-34.10) in the T-DM1 group vs 25.9 months (95% CI, 22.7-28.3) in the control XL group. Median PFS was 9.6 months in the T-DM1 group and 6.4 months in the XL group (HR, 0.65 [95% CI, 0.55-0.77]; P<.0001).[53]

A retrospective exploratory analysis of the patients with stable BrMs in EMILIA characterized the incidence of BrMs after treatment and the efficacy of treatment among patients with pre-existing BrMs. Of 991 randomized patients, 95 had BrMs at baseline. Among the patients with BrMs at baseline, a significant improvement in OS was observed in the T-DM1 arm in comparison with the XL arm (HR, 0.38; P=.008; median, 26.8 vs 12.9 months].[54] PFS was similar in the 2 treatment arms (HR, 1.00; P=1.000; median, 5.9 vs 5.7 months).[54] Although the rates of CNS progression were similar in the T-DM1 and XL arms, in the patients with treated, asymptomatic BrMs, T-DM1 was associated with significantly improved OS in comparison with XL. The low incidence of CNS progression in the patients without BrMs at baseline may be due, in part, to continued HER2 tumor suppression, which potentially contributes to the delayed development of BrMs by controlling extracranial disease.[25,55] Moreover, the permeability of the BBB may be increased with the development of BrMs, facilitating drug uptake and allowing greater local control.[43]

Another trial, KAMILLA, was a phase 3b study of T-DM1 in patients with locally advanced/metastatic HER2+ BC previously treated with HER2-targeted therapy and chemotherapy.[56] Patients with controlled BrMs treated with radiotherapy more than 14 days before enrollment were eligible, as were those with untreated, asymptomatic BrMs. Of 2002 treated patients, 398 had baseline BrMs. A reduction in the sum of the major diameters of the BrMs of at least 30% was noted in 42.9% of the patients, including 49.3% of 67 patients without prior radiotherapy to their BrMs. In the 398 patients with baseline BrMs, median PFS and OS were 5.5 months and 18.9 months, respectively. Similarly, a DESTINY-Breast03 subgroup analysis showed that the 36 patients with BrMs treated with T-DM1 had a 33.4% intracranial response rate, with 1 complete response.[40] In comparison, the patients treated with T-DXd had a 63.9% intracranial response, with 10 of 36 patients experiencing a complete response as per above.

Lapatinib. Lapatinib is a first-generation TKI with activity against endothelial growth factor receptor (EGFR)/HER2 and the first therapy to have shown activity in HER2+ BrMs. When given as a single agent, lapatinib led to few intracranial responses (2%-6%) and only a small, nonsignificant decrease in the size of BrM lesions.[57,58] The LANDSCAPE trial evaluated the combination of lapatinib plus capecitabine (XL) as first-line therapy to 45 patients with low-volume HER2+ BrMs. The objective CNS response was 65.9%, the median time to CNS progression was 5.5 months, and the median time to WBRT was 8.5 months.[59] However, this treatment was associated with a grade 3 to 4 toxicity rate of 49%; toxicities were mainly diarrhea, hand-foot syndrome, and fatigue. In several prospective trials, lapatinib—as a single agent or combined with capecitabine—demonstrated some activity in HER2+ BrMs.[57,59,60] The activity of XL following progression on tucatinib, capecitabine, and trastuzumab is unknown.

Neratinib. Neratinib is an oral and irreversible TKI that inhibits HER1, HER2, and HER4. Neratinib demonstrated benefit in BrMs in the phase 3 NALA trial.[61] In this trial of 621 patients, neratinib plus capecitabine significantly reduced the cumulative incidence of therapeutic interventions for BrMs in comparison with XL after 2 or more HER2-directed therapies for metastatic disease. The overall cumulative incidence of interventions for BrMs was 22.8% for neratinib vs 29.2% for lapatinib (P=.043).[61] Overall, 130 of 621 patients had interventions for BrMs—55 (17.9%) in the neratinib group and 75 (23.9%) in the lapatinib group.[61] The activity of

neratinib/capecitabine following progression on tucatinib, capecitabine, and trastuzumab is unknown. Results of preclinical work recently presented at SABCS 2021 suggest that the combination of neratinib and lapatinib is effective in tucatinib-resistant disease, although neratinib-resistant disease appears also to be resistant to tucatinib.[62] Neratinib is known to have activity in patients with HER2 mutations,[63] which are present in approximately 7% of HER2+ tumors.[64]

Chemotherapy Plus Trastuzumab. Historically, and before the advent of HER2-targeted TKIs and ADCs, trastuzumab was combined with standard cytotoxic chemotherapies. Examples include combination therapy with carboplatin and trastuzumab coupled with bevacizumab, a monoclonal antibody that targets vascular endothelial growth factor receptor (VEGF). In a single-arm phase 2 study of this form of combination therapy among patients with HER2+ (n=29) or HER2– (n=9; without trastuzumab) progressive BrMs, the intracranial response rates were 66% and 56%, respectively.[63] In addition, intracranial tumor concentrations have been higher with nanoparticle drug delivery platforms, including liposomes, than with non-nanoparticle formulations of chemotherapy alone in preclinical models of BC BrMs.[65] A retrospective analysis found that pegylated liposomal doxorubicin in combination with cyclophosphamide in patients with BC BrMs yielded response rates of 41% and disease control rates of 58%.[66] Given the clinical availability of HER2-targeted agents, cytotoxic chemotherapy is less frequently recommended in the setting of advanced HER2+ BC, with or without BrMs.

High-Dose Trastuzumab. A more recent study, the phase 2 PATRICIA trial, assessed pertuzumab plus high-dose trastuzumab in patients with progressive BrMs and HER2+ metastatic BC. Although the CNS ORR was only 11%, the clinical benefit rate in the CNS was 68% at 4 months and 51% at 6 months, with 2 patients having stable disease for more than 2 years.[67] Clinical benefit was also observed in patients with prior exposure to T-DM1, lapatinib, and/or neratinib.[67] No new safety signals were observed. Although the ORR was modest, this combination may have clinical utility in some heavily pretreated patients with progressive BrMs.

Novel Agents

Several novel agents are in clinical development (see eTable at www.hematologyandoncology.net) for HER2+ BC, including several with a known or suspected ability to cross the BBB and yield intracranial efficacy.

GDC-0084. GDC-0084, also known as paxalisib, is a brain-penetrant dual inhibitor of phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR).[68] Previous studies have shown that the PI3K/Akt/mTOR pathway is activated in up to 70% of BC BrMs, but no approved agents targeting this pathway are available for patients with HER2+ BC.[69] A preclinical study investigated the efficacy of PI3K/mTOR blockade with GDC-0084 in BC BrMs and found that this drug is a promising treatment option as monotherapy in models with PIK3CA-activating mutations, including HER2+ models.[70] A phase 2 trial (NCT03765983) is currently underway in patients with HER2+ BC BrMs to investigate combined GDC-0084 and trastuzumab. Of note, all patients with HER2+ BC BrMs are eligible for this trial, regardless of PIK3CA status. Results are anticipated in 2026.

ARX788. ARX788 is an ADC consisting of a monoclonal antibody against HER2 and a payload of AS269, which is a powerful tubulin inhibitor. In previous preclinical studies, this drug has shown promising activity in both HER2+ and HER2-low disease.[71] Recently, at the 2021 ASCO Annual Meeting, the results of 2 phase 1 clinical trials of ARX788 were presented.[72] The ACE-Breast-01 trial included 69 patients with HER2+ BC, and the ACE-Pan Tumor-01 trial included 34 patients with advanced solid tumors; both trials assessed the safety, activity, and pharmacokinetics of ARX788.[72] ARX788 was well tolerated, with impressive efficacy in both studies. In ACE-Breast-01, despite patients being heavily pretreated (median of 6 prior therapy lines), the ORR was 74% (14/19); reported grade 3 or higher toxicities included ocular adverse events (5.7%), pneumonitis (4.3%), and thrombocytopenia (1.4%).[72] Similarly, in the ACE-Pan Tumor-01 trial, the ORR was 67% (2/3); reported grade 3 or higher events were pneumonitis (2.9%) and fatigue (2.9%).[72] Both studies had a disease control rate of 100%, and the median duration of response and PFS data were in progress. A phase 2 trial (NCT05018702) is currently investigating ARX788 in patients with HER2+ BC BrMs that have progressed on TDM-1 as well as in patients with HER2-low tumors who are otherwise ineligible for HER2-directed therapies. Results are anticipated in 2023.

DZD1516. DZD1516 is an oral HER2 TKI that has been shown to be highly BBB-penetrable in preclinical models.[73] It is currently being studied in a phase 1 clinical trial of patients with HER2+ BC BrMs (NCT04509596). Preliminary results, which were reported at SABCS 2021,[73] showed strong inhibition of HER2, with a half-maximal inhibitory concentration (IC_{50}) of 4.4 nM.[73] DZD1516 had a strong affinity for phosphorylated (activated) HER2, and inhibited phosphorylated HER2 with greater than 300-fold selectivity over phosphorylated HER1/

EGFR. Results in vivo were also promising. In xenograft models, a significant tumor response was observed in models of both HER2+ BC BrMs and leptomeningeal disease.[73] The preliminary results showed that the drug was well tolerated overall in patients, with no dose-limiting toxicities. Further analysis of this drug is ongoing.

HER2+ Leptomeningeal Metastases

Leptomeningeal metastases (LMs) occur in approximately 5% to 15% of patients with metastatic BC[74,75] and are a devastating diagnosis. They have a significant effect on quality of life and carry a dismal prognosis; the median survival of patients with HER2+ BC LMs is 4.4 months.[76]

Intrathecal trastuzumab is one of the recognized treatments for HER2+ BC LMs. It can be used either alone or in combination with other systemic therapies. In a recent meta-analysis of intrathecal trastuzumab in patients with LMs, a meaningful clinical improvement was seen in 55%, and 14% had stabilization of disease. On MRI, 70.8% of patients had either stable or improved disease. The iPFS was 5.2 months, and the median OS was 13.2 months.[77]

A recent study, TBCRC049, demonstrated evidence of the distribution of tucatinib into the cerebrospinal fluid (CSF) of patients who had HER2+ metastatic BC with LMs.[78] When the CSF of patients was analyzed 2 hours after the administration of tucatinib, both tucatinib and its major metabolite, ONT-993, were detectable. The CSF-to-plasma unbound concentration ratios were consistent over time.[78] This was the first clinical study that evaluated the distribution of tucatinib into the CSF. Data on the efficacy of tucatinib, trastuzumab, and capecitabine in patients with LMs are forthcoming (NCT03501979; see eTable), but this study is an encouraging step in the treatment of LMs.

Prevention of Brain Metastases

At this time, no systemic therapies in the neoadjuvant/adjuvant or metastatic setting specifically for the primary or secondary prevention of BrMs have been approved, despite high rates of development. This is an evolving field of research, and several trials assessing potential preventative strategies are underway.

The ExteNET trial was a large phase 3 trial that investigated neratinib given as additional adjuvant therapy for 1 year vs placebo after the completion of standard-of-care-treatment, including chemotherapy and trastuzumab.[79] The addition of neratinib for 1 year significantly improved invasive disease–free survival (iDFS) in patients with HER2+ BC. After 5 years of follow-up, a 5.1% iDFS benefit with neratinib in comparison with placebo was noted in patients who had received neratinib within 1 year of prior trastuzumab. In those who had started neratinib more than 1 year after trastuzumab, the iDFS benefit was reduced to 1.3%.[80] An additional finding was that neratinib may be effective in preventing CNS events. At 5 years, the cumulative incidence of first CNS recurrences was 0.7% with neratinib vs 2.1% with placebo. A total of 98.4% of neratinib-treated patients vs 95.7% of patients treated with placebo were alive and without CNS recurrence at 5 years.[80]

Several clinical trials of secondary prevention of BC BrMs are ongoing, with some focused on systemic therapy and HER2+ disease (see eTable). One current trial (NCT03190967) is an open-label, randomized phase 1/2 study of T-DM1 alone vs T-DM1 with metronomic temozolomide. NeraBrain (NCT04856475) is another trial investigating the secondary prevention of HER2+ BrMs. This open-label, single-arm phase 2 study will treat participants with neratinib added to standard of care to assess secondary prevention. Pending the results of these 2 studies, in addition to other trials investigating prophylactic radiation, we may see new approaches to the treatment of HER2+ BrMs in the near future, enabling proactive intervention.

Summary

Despite major advances in systemic therapies for early-stage and advanced HER2+ BC, the development of BrMs remains a significant clinical problem. The recent inclusion of patients with HER2+ BrMs in early- and later-phase clinical trials of brain-penetrable, HER2-targeting systemic therapies has dramatically increased treatment options for patients. T-DXd is now the standard second-line therapy, with activity superior to that of T-DM1 in patients who have stable BrMs. Tucatinib/trastuzumab/capecitabine has robust intracranial activity in patients with stable, untreated, or treated/progressive BrMs, demonstrating benefits in both PFS and OS in comparison with capecitabine/trastuzumab. This regimen is our recommendation for the second-line and later treatment of patients with predominantly active CNS disease. The activity of all therapies beyond progression on T-DXd remains unknown, although many options exist. Clinical trials of HER2+ BrM screening and secondary prevention are underway. We hope that approaches to the treatment of HER2+ BrMs will continue to evolve drastically and improve outcomes for our patients over the coming years.

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Supporting Online Material for "Systemic Management of Brain Metastases in HER2+ Breast Cancer in 2022"

eTable. Recruiting or Not-Yet-Recruiting Clinical Trials Focused on Systemic Treatment of HER2+ Breast Cancer Brain Metastases

Trial Name, Identifier (Phase)	Intervention(s)	Eligibility	Drug Class(es)	Primary Endpoint(s)
iCAR, NCT02442297 (1)	• HER2 CAR T cells	• HER2+ solid tumor metastatic to CNS	• IO	• DLTs incidence
HER2-CAR T Cells in Treating Patients With Recurrent Brain or Leptomeningeal Metastases, NCT03696030 (1)	• HER2 CAR T cells	• Treated, recurrent, or untreated BrMs • HER2+ cancer	• IO	• DLTs incidence • Treatment-related AEs (CTCAE v5.0)
Trial of ZN-A-1041 Enteric Capsules in Patients With HER2-Positive Advanced Solid Tumors, NCT04487236 (1)	• ZN-A-1041 + cape	Phase 1c: • ≥1 measurable BrMs • No immediate local treatment required	• TKI (HER2)	• Safety of ZN-A-1041 + cape at RP2D
T-DM1 Alone Versus T-DM1 and Metronomic Temozolomide in Secondary Prevention of HER2-Positive Breast Cancer Brain Metastases Following Stereotactic Radiosurgery, NCT03190967 (1/2)	• Phase 1: T-DM1 + TMZ • Phase 2: T-DM1 ± TMZ (randomized)	• Phase 1: Any number of BrMs treated with SRS/WBRT • Phase 2: ≤10 BrMs treated with SRS and/or resection	• ADC (HER2) ± alkylating agent	• MTD of temozolomide with T-DM1 • mPFS
HKI-272 for HER2-Positive Breast Cancer and Brain Metastases, NCT01494662 (2)	Different cohorts receiving: • Neratinib • Neratinib + cape • Neratinib + T-DM1	Cohort dependent: • Resectable BrMs • Unresectable BrMs	• TKI (HER2) • TKI (HER2) + antimetabolite • TKI (HER2) + ADC (HER2)	• CNS ORR
GDC-0084 in Combination With Trastuzumab for Patients With HER2-Positive Breast Cancer Brain Metastases, NCT03765983 (2)	• Trastuzumab + GDC-0084	• ≥1 measurable BrMs ≥10 mm • Untreated, treated, or progressive BrMs	• mAb (HER2) + TKI (PI3K/mTOR)	• CNS ORR (RANO-BM) • Correlation of p-4EBP1 in BrMs and response in PDX model
A Study of Pyrotinib Plus Vinorelbine in Patients With Brain Metastases From HER2-positive Metastatic Breast Cancer, NCT03933982 (2)	• Pyrotinib + vinorelbine	• ≥1 BrMs ≥1 cm • Controlled CNS symptoms • No previous WBRT	• TKI + alkaloid agent	• CNS ORR (RANO-BM)
A Multi-cohort Phase II Study of HER2-positive and Triple-negative Breast Cancer Brain Metastases, NCT04303988 (2)	• Pyrotinib + TMZ	• HER2+ BC • Previously received trast + taxanes • ≥1 BrMs ≥1.0 cm	• TKI + alkylating agent	• CNS ORR (RANO-BM)
Palbociclib, Trastuzumab, Lapatinib and Fulvestrant Treatment in Patients With Brain Metastasis From ER Positive, HER-2 Positive Breast Cancer: A Multi-center, Prospective Study in China, NCT04334330 (2)	• Palbociclib + trast + lap + fulvestrant	• ER+, HER2+ BC • ≥1 BrMs measuring ≥10 mm	• TKI (CDK4/6) + mAb (HER2) + TKI (HER2) + SERD	• CNS ORR (RANO-BM)
DEBBRAH, NCT04420598 (2)	• (Fam-) trast deruxtecan (DS-8201, T-DXd)	• ≥1 BrMs ≥10 mm • Nonprogressing, asymptomatic, or new/progressing BrMs	• ADC (HER2)	• 16-wk PFS • CNS ORR (RANO-BM)

eTable. *(Continued)* Recruiting or Not-Yet-Recruiting Clinical Trials Focused on Systemic Treatment of HER2+ Breast Cancer Brain Metastases

Trial Name, Identifier (Phase)	Intervention(s)	Eligibility	Drug Class(es)	Primary Endpoint(s)
TUXEDO-1, NCT04752059 (2)	• (Fam-) trast deruxtecan (DS-8201, T-DXd)	• HER2+ BC • Newly diagnosed BrMs, or BrMs progressing after local therapy • Measurable disease by RANO-BM	• ADC (HER2)	• RR of BrMs (RANO-BM)
TOPAZ, NCT04512261 (1b/2)	• Tucatinib[a] + pembrolizumab + trast	• HER2+ BC • Untreated or previously treated and progressing CNS disease	• TKI (rev), chemo, IO, mAb	• 24-wk CNS disease control rate • Recommended dose of tucatinib
Tucatinib, Trastuzumab, and Capecitabine for the Treatment of HER2+ LMD, NCT03501979 (2)	• Tucatinib[a] + cape + trast	• HER2+ BC • Evidence of LMD by (a) positive CSF cytology or (b) MRI evidence plus clinical signs/symptoms • Stable dose steroids >5 d	• TKI (rev), chemo, mAb	• OS
DESTINY-Breast12, NCT04739761 (3b/4)	• (Fam-) trast deruxtecan (DS-8201, T-DXd)	• HER2+ BC • Untreated or treated stable or progressing BrMs • ≥7 d since SRS/GK; ≥21 d since WBRT	• ADC (HER2)	• ORR in participants without BrMs at baseline • PFS in participants with BrMs at baseline
HER2BRAIN, NCT04760431 (2)	• Trast + taxane + pert vs • Trast + taxane + TKI (pyrotinib, neratinib, or tucatinib)	• HER2+ BC • Progressive BrMs	• mAbs (HER2) + chemo vs • mAb (HER2) + chemo + TKI	• CNS ORR
ARX788 in HER2-positive Breast Cancer Patients With Brain Metastases, NCT05018702 (2)	• ARX788	• HER2+ BC • Previously treated with trast, taxane, and EGFR TKIs • At least 1 untreated parenchymal BrMs	• ADC	• CNS CBR
HER2BAT, NCT04158947 (2)	• T-DM1 + afatinib vs • T-DM1	• HER2+ BC • At least one measurable, progressive BrM after HER2 inhibitor	• ADC + TKI (irrev) vs • ADC	• RP2D • ORR
Pyrotinib, Trastuzumab And Abraxane in HER2-positive MBC With Brain Metastasis, NCT04639271 (2)	• Pyrotinib + trast + abraxane	• HER2+ BC • At least one measurable BrM	• TKI + mAb + chemo	• iORR • iPFS
NeraBrain, NCT04856475 (2)	• Neratinib	• HER2+ BC • Treated, progressive, measurable BrMs (cohort 1) • New BrMs (cohort 2) • LMD (cohort 3)	• TKI	• Time to CNS event (cohort 1) • CNS ORR (cohort 2) • CNS PFS (cohort 3)

eTable. *(Continued)* Recruiting or Not-Yet-Recruiting Clinical Trials Focused on Systemic Treatment of HER2+ Breast Cancer Brain Metastases

Trial Name, Identifier (Phase)	Intervention(s)	Eligibility	Drug Class(es)	Primary Endpoint(s)
InTTercePT, NCT05041842 (2)	• Tucatinib + pert + trast	• HER2+ BC • Isolated brain progression (new or progressive BrMs) on pert/trast	• TKI + mAbs (HER2)	• PFS
DZD1516 in Combination With Trastuzumab and Capecitabine, or in Combination With T-DM1, in Patients With Metastatic HER2 Positive Breast Cancer, NCT04509596 (1)	• DZD1516 + trast ± cape vs • DZD1516 + T-DM1	• HER2+ BC • At least 1 measurable BrM	• TKI + mAb (HER2) ± chemo vs • TKI + ADC	• AEs, SAEs incidence • DLTs • MTD • RP2D of DZD1516 in combinations
HER2CLIMB-04, NCT04539938 (2)	• Tucatinib + T-DXd	• HER2+ BC • Received ≥2 prior HER2-based regimens in metastatic setting • Patients with BrMs, including active BrMs	• TKI + ADC	• Safety, AEs • ORR

[a]FDA-approved for BC BrMs.

ADC, antibody-drug conjugate; AE, adverse event; BC, breast cancer; BrMs, brain metastases; cape, capecitabine; CAR, chimeric antigen receptor; CBR, clinical benefit rate; CNS, central nervous system; CSF, cerebrospinal fluid; CTCAE, Common Terminology Criteria for Adverse Events; d, day(s); DLTs, dose-limiting toxicities; EGFR TKIs, epidermal growth factor tyrosine kinase inhibitors; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; IO, immunotherapy; iORR, intracranial overall response rate; iPFS, intracranial progression-free survival; irrev, irreversible; lap, lapatinib; LMD, leptomeningeal disease; mAb, monoclonal antibody; mPFS, median progression-free survival; MRI, magnetic resonance imaging; MTD, maximum tolerated dose; OS, overall survival; p-4EBP1, phosphorylated 4E-binding protein 1; PDX, patient-derived xenograft; pert, pertuzumab; PI3K/mTOR, phosphoinositide 3-kinase (PI3K)/mammalian target of rapamycin (mTOR); rev, reversible; RANO-BM, response assessment in neuro-oncology brain metastases (criteria); RP2D, recommended phase 2 dosing; RR, response rate; SAE, serious adverse event; SERD, selective estrogen receptor degrader; SRS/GK, stereotactic radiosurgery/gamma knife; T-DM1, trastuzumab emtansine; T-DXd, trastuzumab deruxtecan; TKI, tyrosine kinase inhibitor (see review[83]); TMZ, temozolomide; trast, trastuzumab; wk, week(s); WBRT, whole-brain radiation therapy.