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REVIEW

Management of brain metastases in breast cancer: a review of current practices and emerging treatments

Matthew N. Mills[1] · Nicholas B. Figura[1] · John A. Arrington[2] · Hsiang-Hsuan Michael Yu[1] · Arnold B. Etame[3] · Michael A. Vogelbaum[3] · Hatem Soliman[4] · Brian J. Czerniecki[4] · Peter A. Forsyth[3] · Hyo S. Han[4] · Kamran A. Ahmed[1]

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Abstract

Purpose Breast cancer brain metastases (BCBM) are becoming an increasingly common diagnosis due to improved systemic control and more routine surveillance imaging. Treatment continues to require a multidisciplinary approach managing systemic and intracranial disease burden. Although, improvements have been made in the diagnosis and management of BCBM, brain metastasis patients continue to pose a challenge for practitioners.

Methods In this review, a group of medical oncologists, radiation oncologists, radiologists, breast surgeons, and neurosurgeons specializing in the treatment of breast cancer reviewed the available published literature and compiled a comprehensive review on the current state of BCBM.

Results We discuss the pathogenesis, epidemiology, diagnosis, treatment options (including systemic, surgical, and radiotherapy treatment modalities), and treatment response evaluation for BCBM. Furthermore, we discuss the ongoing prospective trials enrolling BCBM patients and their biologic rationale.

Conclusions BCBM management is an increasing clinical concern. Multidisciplinary management combining the strengths of surgical, systemic, and radiation treatment modalities with prospective trials incorporating knowledge from the basic and translational sciences will ultimately lead to improved clinical outcomes for BCBM patients.

Keywords Breast cancer brain metastases · Stereotactic radiation · Immunotherapy · Blood–brain barrier · Blood-tumor barrier

Introduction

The development of brain metastases from breast cancer has become an increasingly common occurrence due to improvements in systemic therapy and advances in imaging techniques [93]. Breast cancer accounts for roughly 17% of brain metastases, the second most common cause after lung cancer [93, 146]. Approximately 15–30% of breast cancer patients will develop brain metastases during the course of their disease [113, 130]. Although a multitude of systemic treatment options exist for extracranial breast metastases, brain metastases continue to pose management challenges due to the myriad of treatment options available, which require a patient-specific multidisciplinary approach involving medical oncology, radiation oncology, and neurosurgery for optimal management. In this review, we discuss the current approach to diagnosis, multidisciplinary management, and future directions for treatment.

✉ Kamran A. Ahmed
kamran.ahmed@moffitt.org

[1] Department of Radiation Oncology, H. Lee Moffitt Cancer Center and Research Institute, 12902 Magnolia Dr, Tampa, FL 33612, USA

[2] Department of Radiology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA

[3] Department of Neuro-Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA

[4] Department of Breast Oncology, H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL 33612, USA

Prognosis

Efforts to ascertain which patients are at an increased risk for central nervous system (CNS) involvement have identified human epidermal growth factor receptor 2 (HER2) positivity, triple-negative (TN) tumors, young age, lymph node involvement, high grade, and increased tumor size as significant risk factors [41, 51, 52]. There is significant heterogeneity within the clinical outcomes for patients with breast cancer brain metastasis (BCBM), as the median overall survival (OS) ranges from 3 to 26 months [127]. There are multiple prognostic models for patients who develop brain metastasis, including the Recursive Partitioning Analysis (RPA) [42] and the Graded Prognostic Assessment (GPA) [122], which both identified age, performance status, and extracranial disease as significant prognostic factors. Studies have established that receptor status can stratify clinical outcomes, as TN tumors have relatively poor OS, with a median of 3–6 months, while HER2-positive tumors had significantly improved outcomes due to targeted therapy, with a median OS of 11–18 months [28, 65, 85, 94, 117, 145]. The most recent breast cancer-specific prognostic model, the Modified Breast GPA, confirmed that tumor receptor status, along with age, performance status, and number of brain metastases, predicted OS [127].

Diagnosis and screening

Current NCCN guidelines recommend brain MRI screening for recurrent or stage IV breast cancer patients only if symptoms are present [87]. This differs from recommendations for SCLC, stage ≥ II non-small-cell lung cancer (NSCLC), as well as stage IIIC–IV melanoma [88–90]. As the CNS has been an increasing site of failure of breast cancer due to improved systemic control, particularly in HER2 + and TN tumors, there may be a role for routine brain MRI screening in advanced and recurrent breast cancer. A study by Martin et al. reviewed the experience of breast and NSCLC brain metastases management and found that breast cancer patients at initial brain metastases diagnosis were noted to have larger and more numerous brain metastases compared to NSCLC brain metastases [77]. In addition, breast cancer patients were more likely to have symptoms at diagnosis including seizures, leptomeningeal disease, and brainstem involvement. Due to more numerous, larger, and symptomatic brain metastases, breast cancer patients compared to NSCLC patients were more likely to receive whole brain compared to stereotactic radiation. Given these findings, the role of screening brain MRIs, particularly in higher risk populations, should be brought into question. Current prospective trials are studying the role of screening MRIs in breast cancer of various subtypes (clinicaltrials.gov identifier: NCT04030507) and in HER2 + and triple-negative subtypes (NCT03881605).

Breast cancer and the brain microenvironment

The importance of the dynamic interactions within the tumor microenvironment has been established for multiple cancers, and improved understanding of these complex interactions has the potential to aid the search for effective BCBM treatment [143]. However, relatively little is known about the tumor microenvironment within the brain, a setting with obstacles unique to any other metastatic site. Perhaps the most distinctive feature of the CNS is the blood–brain barrier (BBB), a selective diffusion barrier of the cerebral microvascular endothelium that poses a significant obstacle to CNS penetration for metastases [110]. However, tumor cell extravasation in the brain is possible through a variety of mechanisms [14, 61, 124]. Key mediators of CNS penetration for BCBM include the cyclooxygenase COX2, the epidermal growth factor (EGFR) ligand HBEGF, the α2,6-sialyltransferase ST6GALNAC5, and specific matrix metalloproteinases, among others [14, 124]. The ability for tumor cells to cross the BBB, along with the significant delay between the first appearance of circulating tumor cells and the detection of brain metastasis, suggests that tumor colonization within the brain is a crucial step of metastasis formation [134].

Successful colonization depends upon the interactions of tumor cells with unique supportive glial cells of the CNS, microglia and astrocytes [39, 107, 134]. Xing et al. demonstrated that brain metastases expressing a high level of c-Met, a receptor tyrosine kinase, induce a feed-forward cycle of cytokine release with tumor-associated astrocytes that created a favorable microenvironment for tumor cells [147]. Another study found that upregulated c-Met signaling and expression was associated with radioresistance in BCBM cells [149]. Targeting c-Met alone reduced tumor growth, and in combination with radiotherapy, prolonged survival in a murine model [147, 149]. Sikisoon et al. investigated the role of truncated glioma-associated oncogene homolog 1 (TGLI1), a transcription factor associated with angiogenesis, migration, and invasion, in BCBM [118]. Two murine models showed that increased activation of TGLI1 was associated with HER2 + and TNBC, relative radioresistance, and a shortened time to development of BCBM. Astrocyte activation played a significant role in the role of TGLI1 in BCBM formation.

Studies have also demonstrated important interactions between brain metastases and neurons [139]. Neman et al. found that BCBM cells displayed high expression

of gamma-Aminobutyric acid (GABA) receptors, transporters, and transaminase, similar to neuronal cells [92]. This increased expression allowed metastases to catabolize GABA and form nicotinamide adenine dinucleotide (NADH), which increased cell proliferation. Zeng et al. demonstrated that triple-negative BCBMs hijack a neuronal signaling pathway by expressing *N*-methyl-D-aspartate receptors (NMDARs), which are activated by high amounts of glutamate within neuronal synapses [150]. This NMDAR signaling was shown to promote brain colonization and metastasis growth.

Treatment response evaluation

The assessment of treatment response for patients with brain metastasis after radiotherapy may be challenging. Post-radiation effects, such as pseudoprogression, a transient disruption to myelin synthesis and radiation necrosis, necrotic lesions that cause mass effect and neurologic dysfunction, can mimic tumor recurrence upon post-treatment magnetic resonance imaging (MRI) [100]. There has been recent interest in functional imaging methods, such as diffusion weight imaging (DWI), dynamic susceptibility-weighted contrast-enhanced (DSC) MR imaging, and dynamic contrast-enhanced (DCE) MR imaging, to better differentiate between tumor recurrence and radiation treatment effects [141]. Quantitative analysis of post-treatment positron emission tomography (PET) and MRI scans have shown potential to improve the diagnostic accuracy of brain metastasis recurrence as well [71, 72]. However, these methods lack prospective validation. Post-radiation response evaluation remains a challenge, and accurate differentiation between radiation necrosis, pseudoprogression, and true recurrence relies upon clinical assessment and repeated imaging exams [100, 141].

A critical component in the search for new treatments for BCBM patients is the establishment of a consistent treatment response evaluation criteria. The Response Assessment in Neuro-Oncology (RANO) group developed response criteria specifically for brain metastases (RANO-BM), which considers target and non-target lesion response, steroid use, and neurologic symptoms (Table 1) [69]. However, there are important limitations of the RANO-BM in regards to the assessment of progressive disease in patients receiving immunotherapy. Studies have demonstrated that early radiologic findings of disease progression, including increased size of the target lesion or the development of new lesion, do not always accurately predict therapeutic benefit [95]. Therefore, the immunotherapy Response Assessment in Neuro-Oncology (iRANO) criteria were developed to increase the accuracy in identifying true disease progression [96]. For patients who demonstrate radiologic signs of progressive disease without clinical decline and within 6 months of initiating immunotherapy, confirmatory imaging is required 3 months after initial radiologic evidence of progression. The iRANO criteria does require prospective validation prior to widescale adoption.

Local management of BCBM

The treatment options for patients with BCBM have traditionally relied on local approaches including surgery, whole brain radiation therapy (WBRT), and stereotactic radiosurgery (SRS). Surgery can improve survival but is typically reserved for those patients with symptoms, optimal performance status and limited brain metastatic disease [102]. Whether or not they undergo surgical resection, BCBM patients receive radiotherapy. Patients with acceptable performance status and more localized disease undergo SRS, while patients with extensive intracranial disease or poor performance status typically receive WBRT. Traditionally, the role of systemic therapy for BCBM patients has been limited due to the challenges posed by the BBB [31, 70]. However, the role of systemic therapy in management of BCBM patients has rapidly evolved following recent successes in studies managing HER2 + BCBM patients [9, 63, 81].

Surgery

Three randomized clinical trials investigated the additional benefit gained by surgical resection prior to WBRT for patients with a single brain metastasis [80, 102, 140]. One trial conducted by Mintz et al. failed to demonstrate a significant difference in survival or Karnofsky performance status (KPS) between those who received WBRT alone compared to those who received the combination treatment [80]. However, the other two trials demonstrated that patients who received surgical resection had improved OS, as well as more rapid improvement and longer duration of functional independence improvement [102, 140]. Therefore, patients with acceptable performance status and limited extracranial disease are advised to undergo resection followed by radiotherapy, and there's evidence that those patients with symptomatic large lesions (≥ 3 cm in diameter) will benefit most from resection [57, 120].

Several studies have called into question whether prior surgical resection followed by stereotactic radiation may raise the risk of nodular leptomeningeal disease. Nodular or pachymeningeal leptomeningeal disease differs from classical leptomeningeal disease, which appears as tumor masses in the extra-axial spaces near the site of surgical resection. This type of leptomeningeal spread is thought to arise directly from microscopic tumor spillage from surgery or in the post-operative period. A change in the practice

Table 1 Comparison of RANO-BM and iRANO response criteria

	Complete response	Partial response	Stable disease	Progressive disease	Confirmation of treatment response required	Confirmation of progressive disease required	Does a new lesion define progressive disease?
iRANO [96]	Disappearance of all enhancing target and non-target lesions for ≥ 4 weeks; no new lesions; no steroids; clinically stable or improved	≥ 30% decrease in sum of longest diameters of target lesions for ≥ 4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved	Does not qualify for complete response, partial response, or progressive disease	≥ 20% increase in the sum of longest diameters of target lesions; or unequivocal progression of enhancing non-target lesions; or new lesions; or substantial clinical decline	Required at least 4 weeks apart	Yes, at ≥ 3 months from the initial radiologic evidence of progressive disease (if ≤ 6 months after the start of immunotherapy and no signs of significant clinical decline)	Only if > 6 months after start of immunotherapy
RANO-BM [69]	Disappearance of all enhancing target and non-target lesions for ≥ 4 weeks; no new lesions; no steroids; clinically stable or improved	≥ 30% decrease in sum of longest diameters of target lesions for ≥ 4 weeks; no new lesions; stable or decreased steroid dose; clinically stable or improved	Does not qualify for complete response, partial response, or progressive disease	≥ 20% increase in the sum of longest diameters of target lesions; or unequivocal progression of enhancing non-target lesions; or new lesions; or substantial clinical decline	Required at least 4 weeks apart	No	Yes

from delivering WBRT rather than focal stereotactic radiation may make this pattern of spread more common [105]. In a study by Cagney et al., the incidence of nodular leptomeningeal disease was noted in 36 (8.4%) of 428 operations, with a higher incidence noted with resection of previously irradiated vs unirradiated metastases ($p = .008$) [21]. Interestingly, pre-operative SRS has been shown to have lower rates of LMD formation compared to post-SRS (2 years: 16.6% vs 3.2%, $p = .010$) [103], though further prospective studies assessing this approach are warranted.

Radiotherapy

Historically, WBRT has been the standard treatment for patients with brain metastasis. Patchel et al. demonstrated the addition of WBRT to surgery improved rates of intracranial recurrence, and while OS was not significantly different between the two arms, WBRT decreased the rates of neurologic death [101]. The role of WBRT has decreased in recent years due to treatment-related toxicities, including somnolence and impairments to short-term memory, and therefore, WBRT is more often utilized for patients with numerous brain metastases and poor performance status. However, there have been attempts to reduce the rates of neurocognitive toxicity. A placebo-controlled trial found that patients treated with WBRT who received memantine, an *N*-methyl-D-aspartate glutamate receptor blocker typically utilized in dementia, had delayed time to cognitive decline and reduced rates of impairments to memory, executive function, and processing speed [18]. RTOG 0933, a single-arm phase II study, found that intensity-modulated radiotherapy (IMRT) techniques to avoid the hippocampus significantly decreased rates of cognitive decline when compared to historical controls of standard WBRT [47]. Preliminary results from the phase III NRG Oncology CC001 trial reveal improved neurocognitive function in the arm randomized to hippocampal avoidance WBRT compared to standard WBRT [46].

The role of SRS for patients with brain metastasis has been expanding due to its highly conformal nature that spares a significant volume of healthy brain tissue combined with high local control rates. A phase III trial found that when compared to observation, post-operative SRS improved local control for patients with 1–3 brain metastases, similar to WBRT [76]. When compared to WBRT, two additional trials demonstrated no significant differences in OS after SRS [16, 59]. While WBRT was associated with improved intracranial progression free survival (PFS), SRS was associated with a lower risk of cognitive decline. SRS may be an option for patients with up to 10 brain metastases, as a prospective observational study conducted across 23 Japanese institutions in over 1100 patients with 1–10 brain metastases treated with SRS demonstrated that OS did not differ between patients with 2 to 4 metastases and those with 5–10 (median OS 10.8 months in both groups) [148]. There were similar rates of toxicity, local control, neurologic death, leptomeningeal dissemination, and use of salvage radiotherapy between the two groups.

There have been multiple trials investigating the utility of treating patients with both WBRT and SRS. In a phase III trial, Andrews et al. demonstrated the addition of SRS to WBRT significantly improved OS for patients with 1–3 brain metastases and good prognosis (GPA 3.5–4.0) [5, 123]. Multiple trials have established that for patients with 4 or fewer brain metastases, the addition of WBRT to SRS improves both local failure and distant brain failure rates [6, 17, 23, 62]. However, when compared to SRS alone, the addition of WBRT increases the risk of neurocognitive toxicity without conferring a benefit to OS [17]. Interestingly, a combined analysis of three prospective trials found that for patients 50 years or younger, the addition of WBRT to SRS did not impact distant brain relapse rates, and patients who received SRS alone had improved OS [114]. Due to these results, the most recent consensus guidelines recommend against adjuvant WBRT following complete resection or SRS in favor of close monitoring for patients with a limited number of brain metastases [120].

Systemic therapy

Drug conjugates

Historically, the focus of BCBM treatment has been local treatment via surgery and/or radiation therapy due to the challenges posed by the BBB [31, 70]. After a metastasis forms, the BBB remnants, called the blood-tumor barrier (BTB), exhibit increased permeability [91]. While BTB permeability is increased with WBRT and surgery, systemic drug penetration is highly variable and rarely reaches cytotoxic concentrations [70, 81].

There have been multiple recent efforts to overcome the barriers posed by the BTB. ANG1005, a peptide-drug conjugate treatment including Angiopep-2 covalently linked to paclitaxel, utilized the low-density lipoprotein receptor-related protein 1 (LRP-1) to cross the BBB [136]. A phase 2 study of patients with metastatic breast cancer and recurrent brain metastasis found that ANG1005 demonstrated clinical activity, with 14% and 57% of patients with partial response and stable disease, respectively [64]. Patients with leptomeningeal carcinomatosis who received ANG1005 had a median OS of 8 months, longer than the historical median of 4 months following traditional treatment. An ongoing phase 3 clinical trial is further investigating the role of ANG1005 in treating patients with HER2-negative breast cancer and newly diagnosed leptomeningeal carcinomatosis and previously treated brain metastasis (NCT03613181).

Etirinotecan pegol (NKTR 102), a next generation topoisomerase-1 inhibitor-polymer conjugate, also enables BBB penetration and allows for the delivery of SN38, the active metabolite of irinotecan. The BEACON phase 3 trial randomized treatment with NKTR-102 compared physician's choice treatment for women with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine [104]. Unfortunately, NKTR-102 did not significantly improve OS. However, a subgroup analysis demonstrated NKTR-102 drastically improved OS for patients with BCBM within the trial, with a median OS of 10 months compared to 4.8 months [26]. An ongoing phase 3 trial, ATTAIN, is underway to further study the efficacy of NKTR-102 for patients with metastatic breast cancer with stable brain metastases. (NCT02915744).

HER2-positive BCBM

HER2 is a member of the EGFR family and a membrane tyrosine kinase. This oncogene is overexpressed in approximately 14% of breast cancers and is associated with higher risk of brain metastasis, as roughly 44% of resected brain metastases are HER2-positive [60, 117, 121]. While this remains an aggressive subset of breast cancer, HER2 targeted therapies have significantly improved rates of OS; however, anti-HER2 therapy has limited CNS penetration. HER2 + positive patients have among the highest rates of brain metastasis failure [7]. Studies show that the CSF concentration of trastuzumab is 1:420 without pretreatment and improves to 1:79 after being treated with radiation or surgery [35, 131]. To circumvent these low concentrations, in the setting of LMD, intrathecal delivery of trastuzumab has been utilized which has shown improvement in OS compared to historical controls in retrospective analyses and in a phase I/II prospective trial [12, 37, 64].

A phase III trial demonstrated that treatment with both trastuzumab and pertuzumab, two HER2-targeted monoclonal antibodies, combined with docetaxel improved both OS and PFS when compared with trastuzumab and docetaxel alone for patients with metastatic HER2-positive breast cancer [129]. While this trial excluded patients with brain metastasis, an exploratory analysis found the addition of pertuzumab delayed the development of CNS metastasis as the first site of progression [128]. A prospective observational study of the registHER, a database of over 1000 patients with HER2-positive breast cancer, found that trastuzumab and chemotherapy both significantly improved OS for patients with CNS metastasis [19]. This improvement in survival is likely due to improvement in extracranial disease control rather than a direct effect on brain metastases [99]. However, there has been recent interest in the utilization of radiotherapy or ultrasound techniques to increase the permeability of the BTB to trastuzumab that warrant continued investigation [98, 125].

There has been promising data for the treatment of metastatic HER2 + breast cancer patients with trastuzumab emtansine (T-DM1), an antibody–drug conjugate with the HER2-targeted antitumor properties of trastuzumab and the cytotoxic activity of DM1, a potent microtubule inhibitor. The EMILIA phase III trial randomized 991 patients with HER2-positive advanced breast cancer to either treatment with either T-DM1 or lapatinib and capecitabine [142]. Patients treated with T-DM1 had superior PFS (median 9.6 months vs 6.4 months, $p < 0.001$), OS (median 30.9 months vs 25.1 months, $p < 0.001$), and objective response rate (ORR) (43.6% vs 30.8%, $p < 0.001$). This trial excluded patients with CNS metastases that were symptomatic or recently treated. However, an exploratory analysis of the 95 patients who had CNS metastasis at baseline demonstrated that, while there were similar rates of CNS progression between the treatment arms, patients treated with T-DM1 had improved OS (median 26.8 months vs 12.9 months, $p = 0.008$), likely via superior extracranial disease control [63]. A recent analysis has questioned whether stereotactic radiation combined with T-DM1 may increase the risk of radionecrosis through T-DM1 targeting reactive astrocytes and increasing radiation-induced cytotoxicity and astrocytic swelling via upregulation of Aquaporin-4 (Aqp4) [126].

Small molecular tyrosine kinase inhibitors that inhibit the HER2 receptor have shown the potential to improve outcomes for HER2-positive breast cancer. One such tyrosine kinase inhibitor (TKI), lapatinib, targets both HER2 and EGFR. Three phase 3 clinical trials have demonstrated that lapatinib-based regimens, especially when combined with trastuzumab, can improve OS and PFS for HER2-positive locally advanced or metastatic breast cancer patients [11, 34, 43]. Lapatinib has the ability to cross the BTB, as concentrations are significantly higher within brain metastases compared to healthy brain tissue [132]. However, the penetration of the BTB is highly variable, and only about 17% of brain metastases demonstrated a lapatinib concentration that approached that of systemic metastases [132]. The LANDSCAPE trial investigated the treatment combination of lapatinib and capecitabine for 45 patients with HER2-positive BCBM not previously treated with WBRT, capecitabine, or lapatinib [9]. The trial demonstrated encouraging results, as 65.9% of patients had a partial CNS response defined as a $\geq 50\%$ response to treatment with a median time to progression of 5.5 months. A phase I trial of HER2 + BCBM patients demonstrated that concurrent WBRT and lapatinib followed by adjuvant lapatinib and trastuzumab can achieve a CNS ORR of 79% and 6-month PFS of 46% [68].

Pooled analysis of two phase 1b studies of tucatinib, another small molecule TKI, in the treatment of metastatic

HER2-positive breast cancer patients identified a subgroup of patients that achieved extended disease control, with a PFS of at least 16 months [48]. Within this subgroup, half of the patients had brain metastasis. Another pooled analysis of the two phase 1b studies demonstrated comparable PFS for patients with and without brain metastasis [83]. Further analysis investigated the outcomes for patients who developed isolated brain progression and received CNS-directed therapy [84]. Those patients that continued on the tucatinib-based regimen, compared to those who discontinued the study, had superior preserved performance status, reduced risk of neurologic adverse events, and a median of 8.3 months to any second event.

The phase 3 ExteNET trial established an additional year of adjuvant neratinib, an irreversible TKI with inhibition of HER1, HER2, and HER4, administered after chemotherapy and trastuzumab, improved invasive disease-free survival for patients with HER2-positive early stage breast cancer [78]. The NEfERT-T phase 3 trial randomized 479 women with previously untreated and/or recurrent or metastatic HER2-positive breast cancer to received neratinib or trastuzumab, each combined with paclitaxel [8]. While there was no significant difference in PFS, the neratinib group did have a lower incidence of CNS recurrence (RR 0.48, $p=0.002$), as well as a longer time to CNS metastasis (HR 0.45, $p=0.004$). A phase 2 trial of neratinib and capecitabine for patients with HER2 + BCBM demonstrated further evidence of CNS activity, as patients who were lapatinib-naïve achieved a CNS ORR of 49% and a median PFS of 5.5 months [40]. The phase 3 NALA trial, which randomized patients with stage 4 HER2-positive breast cancer to receive neratinib and capecitabine or lapatinib and capecitabine, demonstrated that patients treated in the neratinib arm had a significant improvement in PFS. Interestingly, patients treated with neratinib had decreased rates of CNS disease (22.8% vs 29.2%, $p=0.043$) and delayed time to intervention for symptomatic CNS disease [27].

Afatinib, a novel TKI that targets both EGFR and HER4, has also been used to treat HER2-positive breast cancer. A phase II trial of patients with stage III or inflammatory disease found that for neoadjuvant treatment, afatinib compared favorably with trastuzumab monotherapy and lapatinib monotherapy [111]. However, further trials have demonstrated a suboptimal associated risk benefit ratio. The LUX-Breast 3 phase 2 trial randomized 121 patients with HER2-positive breast cancer and CNS recurrence or progression to treatment with afatinib, afatinib with vinorelbine, or the investigator's choice of treatment [25]. The afatinib-containing regimens had higher rates of toxicity without improvement in patient benefit. Ongoing prospective clinical trials for HER2 + patients are detailed in Table 2.

Hormone-positive BCBM

Endocrine, or hormonal, therapy is an integral component in the treatment of HR + breast cancer at both the early and advanced stages of disease; however, the role of hormonal agents in the treatment of CNS metastases has not been well studied. While tamoxifen is highly lipophilic and able to cross the blood–brain barrier achieving therapeutic concentrations within the CSF, there is reasonable concern for hormonal resistance at time of progression [66]. Approximately 20% of HR + breast cancer patients have a de novo, or primary, resistance to hormone therapy [79], and nearly half of patients will ultimately acquire resistance with prolonged treatment [97]. Furthermore, there is concern whether hormonal therapy would be effective for CNS metastases as the discordance rates of hormone receptor status between the primary and metastatic intracranial tumors is approximately 40% [53, 56].

One therapeutic approach to combat hormonal resistance has been to target the downstream pathways by inhibiting CDK4 and CDK6. CDK4/6 inhibitors, such as abemaciclib, palbociclib, and ribociclib, have been shown to cause cell cycle arrest, decreased cell viability, and apoptosis [106]. Several large prospective trials have demonstrated improved ORR, PFS, and OS in both the endocrine-resistant (MONARCH-2 [119], PALOMA-3 [138]) and the first-line setting (MONARCH-3 [44], PALOMA-2 [38], and MONALEESA 7 [54]) for HR + advanced breast cancer patients.

The efficacy of CDK4/6 inhibitors on CNS metastases is currently unknown. Only the PALOMA-2, PALOMA-3, MONALEESA-3 and MONALEESA7 trials included patients with CNS disease. Preclinical and clinical data have demonstrated the ability of CDK4/6 inhibitors to cross the BBB with variable efficiency [30, 109, 137]. Given CDK4/6 inhibitor's potential benefit and minimal side effects, prospective studies are ongoing to assess the efficacy of abemaciclib (NCT02308020) and palbociclib (NCT02774681) in the treatment of BCBM. Early results of NCT02308020, which were recently published in abstract form, found an intracranial clinical benefit rate of 25% with abemaciclib and a median PFS of 4.4 months in a heavily pretreated patient population [22].

However, preclinical evidence suggests that there may be a synergistic benefit combining CDK inhibitors with radiotherapy [49, 144]. As patients survive longer with improved systemic agents and more frequent imaging identifies a greater number of asymptomatic brain metastases, it is essential to ensure that the synergistic combination of CDK4/6 and RT does not translate to increased toxicities. Two recently published retrospective studies suggest that the early clinical experience in combining CDK4/6 inhibitors and radiotherapy is safe and tolerable. Chowdary et al. reported minimal grade 2 and no grade 3 toxicities in the

Table 2 Ongoing interventional clinical trials for HER2 + breast cancer brain metastasis

Clinical trial number	Title	Phase	Number of patients	Lead	Receptor status	Study intervention	Primary outcome
NCT03696030	A Phase 1 Cellular Immunotherapy Study of Intraventricularly Administered Autologous HER2-Targeted Chimeric Antigen Receptor (HER2-CAR) T Cells in Patients With Brain and/or Leptomeningeal Metastases From HER2 Positive Cancers	I	39	City of Hope Comprehensive Cancer Center	HER2+	Chimeric antigen receptor T cell therapy	Dose limiting toxicity
NCT01921335	Phase I Dose-escalation Trial of ARRY-380 in Combination With Trastuzumab in Participants With Brain Metastases From HER2 + Breast Cancer	I	41	Dana-Farber Cancer Institute	HER2+	ARRY-380, Trastuzumab	MTD
NCT02650752	Phase I Study of Intermittent High-Dose Lapatinib in Tandem With Capecitabine for HER2 Overexpressed/Amplified Metastatic Breast Cancer With Central Nervous System (CNS) Metastases	I	11	Memorial Sloan Kettering Cancer Center, Queens Cancer Center of Queens Hospital, University of Michigan	HER2+	Lapatinib, Capecitabine	MTD
NCT02571530	Phase 1 Trial of Super-selective Intra-arterial Cerebral Infusion of Trastuzumab After Blood–Brain Barrier Disruption for the Treatment of Cerebral Metastases of HER2/Neu Positive Breast Cancer	I	48	Northwell Health	HER2+	Intra-arterial Cerebral Infusion of Trastuzumab	MTD
NCT01783756	Phase 1b/2 Single-arm trial evaluating the combination of Lapatinib, Everolimus and Capecitabine for the treatment of patients with HER2-positive Metastatic Breast Cancer with CNS progression after Trastuzumab	I/II	9	Jonsson Comprehensive Cancer Center	HER2+	Lapatinib ditosylate, everolimus, capecitabine	CNS ORR
NCT03190967	Phase I/II Study of T-DM1 Alone Versus T-DM1 and Metronomic Temozolomide in Secondary Prevention of HER2-Positive Breast Cancer Brain Metastases Following Stereotactic Radiosurgery	I/II	125	National Cancer Institute, National Institutes of Health Clinical Center	HER2+	T-DM1, TMZ	MTD, Median PFS

Table 2 (continued)

Clinical trial number	Title	Phase	Number of patients	Lead	Receptor status	Study intervention	Primary outcome
NCT03933982	Pyrotinib Plus Vinorelbine in Patients With Brain Metastases From HER2-positive Metastatic Breast Cancer: a Prospective, Single-arm, Open-label Study	II	30	Chinese Academy of Medical Sciences	HER2+	Pyrotinib, Vnorelbine	CNS ORR
NCT01494662	A Phase II Trial of HKI-272 (Neratinib), Neratinib and Capecitabine, and Ado-Trastuzumab Emtansine for Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer and Brain Metastases	II	168	Dana-Farber Cancer Institute	HER2+	Neratinib, Capecitabine, Ado-Trastuzumab Emtansine	ORR
NCT03765983	Phase II Trial of GDC-0084 in Combination With Trastuzumab for Patients With HER2-Positive Breast Cancer Brain Metastases	II	47	Dana-Farber Cancer Institute	HER2+	Trastuzumab, GDC-0084	CNS ORR
NCT02536339	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 (PATRICIA)	II	40	Genentech, Inc.	HER2+	Petruzumab, Trastuzumab	CNS ORR
NCT03417544	A Phase II Study of Atezolizumab in Combination With Pertuzumab Plus High-dose Trastuzumab for the Treatment of Central Nervous System Metastases in Patients With Her2-positive Breast Cancer	II	33	Genentech, Inc., Dana-Farber Cancer Institute	HER2+	Atezolizumab, Pertuzumab, Trastuzumab	CNS ORR

Table 2 (continued)

Clinical trial number	Title	Phase	Number of patients	Lead	Receptor status	Study intervention	Primary outcome
NCT01622868	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	II	143	National Cancer Institute, NRG Oncology	HER2+	Lapatinib, SRS, WBRT	CR rate of measurable brain metastases
NCT02774681	A Phase II Single-Arm Study of Palbociclib in Patients With Metastatic HER2-positive Breast Cancer With Brain Metastasis	II	12	Northwestern University	HER2+	Palbociclib, Trastuzumab	CNS ORR
NCT02898727	A Phase II Study of Local Therapy Only (Stereotactic Radiosurgery and/or Surgery) for Treatment of up to 5 Brain Metastases From HER2 Positive Breast Cancer	II	50	Trans-Tasman Radiation Oncology Group (TROG)	HER2+	Resection, SRS	Percentage of Patients requiring WBRT within 12 months
NCT02614794	A Study of Tucatinib vs. Placebo in Combination With Capecitabine and Trastuzumab in Patients With Advanced HER2 + Breast Cancer (HER2CLIMB)	II	612	Seattle Genetics, Inc.	HER2+	Tucatinib, Capecitabine, Trastuzumab	PFS

PFS progression free survival, *HER2* human epidermal growth factor 2, *ORR* overall response rate, *MTD* maximum tolerated dose, *CR* complete response, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiotherapy

Table 3 Ongoing interventional clinical trials for breast cancer brain metastasis

Clinical trial number	Title	Phase	Number of patients	Lead	Receptor status	Study intervention	Primary outcome
NCT02913430	Treatment of metastatic breast cancer with fulvestrant plus palbociclib or tamoxifen plus palbociclib: a randomized phase II trial with ESR1 mutation tested in circulating tumor DNA.	II	150	University of Pittsburgh Cancer Institute	ER+	Fulvestrant, Tamoxifen, Palbociclib	PFS
NCT03637868	A phase II study of eribulin in brain metastases from her2-negative breast cancer pretreated with anthracyclines and taxanes	II	95	Institut Paoli-Calmettes	HER2-	Eribulin Mesylate	CNS ORR
NCT03613181	A randomized open-label, multicenter pivotal study of ANG1005 compared with physician's best choice in HER2-negative breast cancer Patients With newly diagnosed leptomeningeal carcinomatosis and previously treated brain metastases (ANGLeD)	III	150	Angiochem, Inc	HER2-	ANG1005	OS
NCT03709446	A phase I/II trial of leflunomide in women with previously treated metastatic triple-negative cancers	I/II	54	Icahn School of Medicine at Mount Sinai	TN	Leflunomide	MTD, Clinical Benefit Rate
NCT03483012	A phase II study of atezolizumab in combination with stereotactic radiation for patients with triple-negative breast cancer and brain metastasis	II	45	Dana-Farber Cancer Institute	TN	Atezolizumab, SRS	PFS
NCT02595905	Phase II randomized placebo-controlled trial of cisplatin with or without ABT-888 (Veliparib) in metastatic triple-negative breast cancer and/or BRCA mutation-associated breast cancer, with or without brain metastases	II	333	National Cancer Institute	TN or BRCA Mutated	Cisplatin, Veliparib	PFS
NCT01724606	Whole brain radiotherapy (WBRT) with sorafenib for breast cancer brain metastases (BCBM): a phase I study	I	21	Memorial Sloan Kettering Cancer Center		WBRT, Sorefenib	MTD

Table 3 (continued)

Clinical trial number	Title	Phase	Number of patients	Lead	Receptor status	Study intervention	Primary outcome
NCT03661424	A Phase I Study of Anti-CD3 × Anti-Her2/Neu (Her2Bi) Armed Activated T Cells (ATC) in patients with breast cancer leptomeningeal metastases	I	16	University of Virginia		HER2 BATs	Adverse Events
NCT03807765	Stereotactic radiation and Nivolumab in treating patients with breast cancer that has spread to the brain	I	12	Moffitt Cancer Center		SRS, Nivolumab	Dose Limiting Toxicity
NCT03449238	Pembrolizumab and Stereotactic Radiosurgery (SRS) Of selected brain metastases in breast cancer patients	I/II	41	Weill Medical College of Cornell University		Pembrolizumab	Tumor response for non-irradiated brain lesions
NCT02581839	Treatment of brain metastases from breast cancer with eribulin mesylate	II	9	Case Comprehensive Cancer Center		Eribulin Mesylate	CNS PFS
NCT02260531	A phase II study of Cabozantinib alone or in combination with Trastuzumab in breast cancer patients with brain metastases	II	40	Dana-Farber Cancer Institute		Cabozantinib, Trastuzumab	CNS ORR
NCT04061408	A phase II pilot study of Fractionated stereotactic radiotherapy (FSRT) in breast cancer patients with 1–10 brain metastases	II	170	Fudan University		FSRT	Intracranial Local Tumor Control Rate
NCT03328884	Multicenter open-label, phase II trial, to evaluate the efficacy and safety of Nal-IRI for progressing Brain metastases in patients With HER2-negative breast cancer (The Phenomenal Study)	II	63	MedSIR		Irinotecan Hydrochloride	CNS ORR
NCT02185352	Randomized phase II study of induction bevacizumab, etoposide and cisplatin followed by whole brain radiotherapy (WBRT) versus WBRT alone in breast cancer with untreated brain metastases	II	120	National Taiwan University Hospital		Bevacizumab, Etoposide, Cisplatin	Brain-specific PFS

Table 3 (continued)

Clinical trial number	Title	Phase	Number of patients	Lead	Receptor status	Study intervention	Primary outcome
NCT03412955	A pilot study of Eribulin in breast cancer (BC) patients with brain metastases previously treated with anthracyclines and taxanes	II	14	Tan Tock Seng Hospital		Eribulin Mesylate	Objective Tumor Response Rate
NCT03331601	Evaluation of 68GaNOTA-Anti-HER2 VHH1 uptake in brain metastasis of breast carcinoma patients	II	30	Universitair Ziekenhuis Brussel		68GaNOTA-Anti-HER2 VHH1	Tumor-targeting potential in brain metastasis
NCT02000882	Phase II multicenter single-arm study of BKM120 plus capecitabine for breast cancer patients with brain metastases	II	10	US Oncology Research, Novartis Pharmaceuticals		BKM120, Capecitabine, Trastuzumab	Clinical Benefit Ratio
NCT01332630	A phase 2 open-label study of TPI 287 in patients with breast cancer metastatic to the brain	II	24	MD Anderson Cancer Center		TPI 287	ORR
NCT01782274	Proteome-based personalized immunotherapy of brain metastases from breast cancer	II/III	60	NeuroVita Clinic, Blokhin's Russian Cancer Research Center, Russion Foundation of Technological Development		Dendritic vaccine, allogeneic hematopoietic stem cells, cytotoxic lymphocytes	All cause mortality
NCT02915744	A study of etirinotecan pegol (NKTR-102) versus treatment of physician's choice (TPC) in patients with metastatic breast cancer who have stable brain metastases and have been previously treated with an anthracycline, a taxane, and capecitabine	III	178	Nektar therapeutics		NKTR-102 vs TPC	OS

ER estrogen receptor, *PFS* progression free survival, *HER2* human epidermal growth factor 2, *ORR* overall response rate, *OS* overall survival, *MTD* maximum tolerated dose, *CR* complete response, *SRS* stereotactic radiosurgery, *WBRT* whole brain radiotherapy, *TN* triple negative, *FSRT* fractionated stereotactic radiotherapy

16 patients treated with conventionally fractionated radiotherapy, including three who received WBRT [24]. Figura et al. published their single institution experience treating 42 intracranial lesions with stereotactic radiotherapy within 15 patients concurrently taking CDK4/6 inhibitors reporting a 5% rate of radionecrosis, comparable to historical controls with OS that appeared improved [36].

As described above, endocrine resistant HR + breast cancer may proliferate by utilizing alternative cell signaling pathways. Recurrent HR + breast cancer is oftentimes associated with constitutionally active PI3K/AKT/mTOR pathways [1, 15], which may provide a novel therapeutic target in treating HR + BCBM. The use of PI3K inhibitor inhibitors, such as taselisib [20] or mTOR inhibitors, such as everolimus [10], have found to demonstrate a systemic response in prospective studies. Recent in vitro studies have demonstrated the ability for pan-Akt inhibitors to cross the BBB, decreasing tumor cell viability, and inducing apoptosis in BCBM [55]. Multiple prospective studies are currently evaluating their use of combining PI3K/AKT/mTOR and CDK4/6 inhibitors in HR + breast cancer to prevent treatment resistance (NCT03006172, NCT02684032, NCT02389842, NCT02732119, NCT02871791, NCT02599714).

Triple-negative BCBM

Patients with TN breast cancer (TNBC) also have a high risk of CNS failure, and those that do develop CNS metastasis have poor outcomes, with a median survival of 3–6 months [29, 65, 85, 94]. Treatment for these patients is limited by the lack of actionable targets for therapy, as well as the challenges posed by the BTB. A recent murine model demonstrated promising results using an amphiphilic polymer-lipid nanoparticle system to penetrate the BBB and deliver docetaxel to TNBC brain metastases in a murine model [50]. Treatment with the nanoparticle system significantly delayed tumor growth and prolonged survival. Another preclinical study demonstrated BBB penetration and improved outcomes with the combination of carboplatin and veliparib, a small molecule inhibitor of poly ADP-ribose polymerase [58]. Bevacizumab, the vascular endothelial growth factor (VEGF) inhibitor, has shown potential in the treatment of BCBM patients. Phase 2 trials, including TNBC, have demonstrated that bevacizumab can improve CNS response [67, 75]. There is an ongoing phase 2 trial of patients with recurrent or metastatic BRCA mutation associated and/or TNBC with or without brain metastases randomized to treatment with veliparib compared to placebo, both with concurrent cisplatin (NCT02595905) (Table 3).

Immune therapy

Antibody-directed therapies that alter interactions between CTLA-4 and PD-1/programmed death ligand 1 (PD-L1) have proven invaluable in the treatment of multiple cancers, including NSCLC, melanoma, and renal cell cancer [13, 82, 112]. The activity of the immune checkpoint inhibitors is not limited to extracranial disease, as trials have demonstrated significant response in the treatment of brain metastasis within melanoma and NSCLC [45, 133]. A number of clinical trials have also demonstrated that immune checkpoint inhibitors, such as pembrolizumab, nivolumab, and atezolizumab, can improve outcomes within breast cancer [2, 73, 86, 115]. Atezolizumab with nab-paclitaxel is now approved for use in PD-L1 positive locally advanced or metastatic TNBC not amenable to surgical resection [115]. The ability for immunotherapy to benefit patients with metastatic breast cancer, as well as the encouraging data on melanoma and NSCLC brain metastasis response, has sparked interest in investigating immune checkpoint inhibitors in the treatment of BCBM. In addition, studies have revealed constant immune surveillance of the CSF from meningeal lymph nodes with direct communication to the deep cervical nodes [74].

There has been significant interest in combining radiation therapy with immune checkpoint inhibition due to an immune priming effect noted from radiation therapy in preclinical studies noting upregulation of PD-L1 [32, 33] and enhanced tumor reduction and clinical data which have suggested clinical improvement including in the setting of brain metastases [3, 4, 108, 116, 135]. There are currently ongoing phase 2 trials examining the treatment of BCBM via SRS with concurrent Atezolizumab (NCT03483012), Nivolumab (NCT03807765), and Pembrolizumab (NCT03449238).

Conclusions

The significant heterogeneity of outcomes within BCBM implies opportunities to optimize precision treatment for these patients. While the treatment of BCBM has progressed greatly in the past decades, there are many ongoing efforts to improve clinical outcomes. This will continue to require a multidisciplinary approach improving our methods of BCBM screening, surgical and radiation delivery techniques as well as an improved understanding of the underlying biology of brain metastases to improve systemic treatment delivery. As systemic disease treatment continues to improve, simultaneous improvements in BCBM management will be required.

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Compliance with ethical standards

Conflicts of interest Hsiang-Hsuan Michael Yu has received speaker's honoraria from BrainLab and is on the advisory boards of Novocure and Abbvie. Michael A. Vogelbaum has indirect equity and royalty interests in Infuseon Therapeutics, Inc. and has received honoraria from Tocagen, Inc. and Celgene. Hatem Soliman serves as a consultant for Astrazeneca, Celgene, Novartis, PUMA, and Eisai. Brian J. Czerniecki has intellectual property on a HER2 dendritic cell vaccine. Peter A. Forsyth has received research funding from Pfizer and Celgene and is on the advisory boards of Novocure, BTG, Inovio, AbbVie, Ziopharm, Tocagen, and Pfizer. Hyo S. Han declares that she has received a speaker's honorarium from Lilly Pharmaceuticals, research funding to the institution from Abbvie, Tesaro, TapImmune, Novartis, Bristol-Myers Squibb, Pfizer, SeattleGenetics, Prescient, Horizon, and Karyopharm. Kamran A. Ahmed has received research funding from Bristol-Myers Squibb and Genentech.

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