Emerging treatment strategies for breast cancer brain metastasis: from translational therapeutics to real-world experience

Ding Ren*, Hao Cheng*, Xin Wang, Monika Vishnoi, Bin S. Teh, Robert Rostomily, Jenny Chang, Stephen T. Wong and Hong Zhao

Abstract: Systemic therapies for primary breast cancer have made great progress over the past two decades. However, oncologists confront an insidious and particularly difficult problem: in those patients with metastatic breast cancer, up to 50% of human epidermal growth factor 2 (HER2)-positive and 25–40% of triple-negative subtypes, brain metastases (BM) kill most of them. Fortunately, standard-of-care treatments for BM have improved rapidly, with a decline in whole brain radiation therapy and use of fractionated stereotactic radiosurgery as well as targeted therapies and immunotherapies. Meanwhile, advances in fundamental understanding of the basic biological processes of breast cancer BM (BCBM) have led to many novel experimental therapeutic strategies. In this review, we describe the most recent clinical treatment options and emerging experimental therapeutic strategies that have the potential to combat BCBM.

Keywords: breast cancer brain metastasis, emerging treatment strategies, translational therapeutics

Received: 24 March 2020; revised manuscript accepted: 21 May 2020.

Introduction

Brain metastasis (BM) is an indication of poor prognosis for cancer patients with short overall survival and low quality of life.1 The prevalence of breast cancer brain metastasis (BCBM) is increasing as treatment of primary cancers and imaging techniques improve.2 In addition, the brain is a “sanctuary site” for breast cancer cells treated with pharmacological agents that have poor drug penetration into central nervous system (CNS). For example, among patients who received adjuvant trastuzumab (a monoclonal antibody targeting HER2) in the HERA study, the brain made up a larger proportion of initial relapse sites compared with controls.3 Concentration of trastuzumab in cerebrospinal fluid (CSF) was detected to be 420-fold less than in sera of patients treated with trastuzumab before radiotherapy.4 Although small molecules (e.g., neratinib, molar mass: 557.04 g/mol, or afatinib, molar mass: 485.94 g/mol) are more able to across the blood-brain barrier (BBB) than the monoclonal antibody trastuzumab (molar mass: 14,553.15 g/mol),5,6 the discrepancy of treatment response between extracranial disease control and intracranial disease progression was also observed in metastatic HER2-positive patients treated with neratinib or afatinib,7–9 suggesting unique disease biology of BCBM and more complicated vulnerability to targeted therapies.

Indeed, BCBMs residing within the neural microenvironment confront a distinct set of structural (especially the BBB), physiological, and molecular factors, and undergo additional brain-adaptive modifications to support tumor survival and outgrowth. Recent studies focusing on tumor–neural microenvironment interactions have revealed novel therapeutic strategies, especially in repositioning existing drugs to target potent microenvironmental factors that promote tumor growth (Figure 1). Repurposing known drugs for new indications is a promising strategy to accelerate...
drug discovery of unmet medical need such as BCBM. Because of the profiled toxicity and pharmacokinetic information, drugs that are identified through repositioning have the potential for rapid clinical translation. In addition, other emerging clinical treatment options for BCBM patients include novel targeted therapy and immunotherapy, minimally invasive neurosurgery, and stereotactic radiotherapy (Table 1), have shown promise in many clinical studies to improve patient survival and quality of life.

**Targeting tumor–neural microenvironment interactions in BCBM**

As opposed to molecular mechanisms involving cancer cell–host interactions shared by multiple cancer types that result in organ specific metastasis, a highly distinct set of structural, anatomic, physiological, and molecular factors regulate metastasis to the brain. Astrocytes, the most common glial cells comprising ~50% of all human brain cells, are a well-characterized perilesional component of BCBM. Recent discoveries, including ours, provide compelling evidence that molecular crosstalk between astrocytes and cancer cells is integral to BCBM development.

The Valiente group showed in clinical BCBM samples and xenograft mouse models, including HER2+ and triple-negative (TNBC) subtypes, that a subpopulation of reactive astrocytes with activated signal transducer and activator of transcription 3 (STAT3) contributed to the pro-metastatic microenvironment. These STAT3+ astrocytes benefit metastatic breast cancer cells by impeding CD8+ lymphocytic infiltration into the metastatic area through secretion of infiltration-suppressive proteins such as vascular endothelial growth factor A (VEGF-A) and tissue inhibitor of metalloproteinases-1 (TIMP-1), and inhibiting the acquired immune response as they also express programmed cell death 1 ligand 1 (PD-L1). In addition, the STAT3+ astrocytes crosstalk with CD74+ microglia/microphages through the MIF–CD74–midkine signaling axis in promoting the brain metastatic tumor growth. To this end, silibinin, a commercially available nutraceutical that crosses the BBB to impair STAT3 activation, was used to treat BCBM animal models and a cohort of 18 patients. Silibinin alone significantly reduced experimental BM even at advanced stages of colonization. In BCBM patients treated with Silibinin, as a single agent or in combination with additional chemotherapy, the overall response rate was 75% patients, including 3 complete responses (20%) and 10 partial responses (55%). Given the safety profile and oral bioavailability, silibinin supplementation provides great hope to increase survival in BCBM patients.

Recent reports from our group and the Massagué group identified other BCBM-astrocyte crosstalk signaling focusing on protocadherin7 (PCDH7). Using TNBC patient-derived BCBM samples and animal models, we demonstrated that a brain-tropic cancer stem cell population drives tumor metastasis in the brain, and interactions with astrocytes mediated by high PCDH7 expression promoted in vivo tumor growth through PCDH7-PLCβ signaling. Notably, in animal studies immuno-reactive PCDH7 expression was re-detected in brain metastatic lesions in the PCDH7 shRNA group, as well as tumor surrounding astrocytes. The re-expression of PCDH7 in the surviving brain metastatic tumor cells suggests that selection for tumor cell PCDH7 expression promotes cell survival and tumor growth in vivo. In late stage TNBC and HER2+ BCBMs, elevated PCDH7 expression on tumor cells was required to establish PCDH7-Cx43 gap junctions that mediated paracrine signaling between brain metastatic tumor cells and astrocytes. Through the gap junction channel between both cell types, Ca2+ and secondary messenger cGAMP contribute to chemoresistance in BCBM. Cancer cells from TNBC and HER2+ breast cancer cells co-opted the gap junction connection with astrocytes to reduce their excessive calcium burden, for which the excessive intracellular calcium could be detrimental for cancer cells by triggering DNA damage and inducing apoptosis. As a consequence, the decrease of intracellular calcium facilitates resistance to chemotherapy and aggressive colonization in the brain. Reciprocally and initiated by the transfer of second messenger from tumor cells to astrocytes, cGAMP activated astrocytic STING, which leads to phosphorylation of IRF3, and subsequently induced expression and secretion of TNFα and INFα. These two cytokines in turn activated NFκβ and STAT1 in brain metastatic cells that contribute to an accelerated proliferation and resistance to chemotherapeutic stress. Two proof-of-concept therapeutic strategies were verified in the TNBC BCBM animal models, one is the repositioning of edelfosine, a phase II clinical trial drug in treating leukemia with bone marrow transplants that blocks PLCβ, and the other is the
gap junction directed therapy of repositioning meclofenamate, a FDA-approved anti-inflammatory drug that inhibits Cx43 gap junction gating. To recapitulate clinical situation where BM tumors are established before treatment, edelfosine treatment in mice started when micro-metastases were detected (around 10 days post tumor cell inoculation into left ventricle). During a 15-day treatment regimen (i.p., once daily, 30 mg/kg/day), brain metastatic tumor growth was continuously suppressed in the edelfosine group, and it was noted that the formation of macro-metastases (>50 cells) in the treated mice was inhibited by 90% at the end of 15-day treatment (p < 0.01). Activations of cellular PLCγ and Ki-67-positive tumor cell proliferation were repressed remarkably by the edelfosine treatment.16 In the same animal model, meclofenamate (i.p., once daily, 20 mg/kg/day) in combination with chemotherapeutic drug carboplatin profoundly inhibited BM.15

Of importance, in independent studies, shRNA-mediated PCDH7 depletion in TNBC and HER2+ breast cancer cells inhibited brain metastatic growth in immunocompetent and xenograft models. This suggests that PCDH7, a brain-specific gene, may be a robust multi-functional mediator of BCBM-astrocyte crosstalk and a new potential therapeutic target. PCDH7 is a brain-specific gene.31,32

Adult human brain endothelial cells and primary microglia have no detectable, or very low, level of PCDH7 expression.15 Primary astrocytes have moderate expression of PCDH7, whereas astrocyte PCDH7 expression exhibits a dramatic increase in response to the brain metastatic tumor insult.15,16 These data suggest that astrocytic PCDH7 has a pro-metastatic role in BCBM. Pharmacological blocking or targeting the astrocytic PCDH7 may not have profound side-effects on other brain resident cells, especially given that overexpression of PCDH7 inhibits neuronal survival.32 To this end, we are exploring small molecules to block the PCDH7 homophilic and PCDH7-Cx43 heterophilic binding for potential BCBM treatment.

In a series of studies by the Cittelly group, estrogen receptor (ER)-positive astrocytes were pro-metastatic in BM in the TNBC subtype.33,34 Astrocytes express classical ERs (ERα and ERβ). In vitro, estrogen treatment up-regulated epidermal growth factor receptor (EGFR) ligands and brain-derived neurotrophic factor in astrocytes and activated EGFR and tropomyosin kinase receptor B in TNBC brain metastatic cells. Estrogen also stimulated release of astrocyte-derived paracrine factors to promote tumor proliferation. In TNBC BCBM mouse models, ovariectomy decreased the magnetic resonance imaging (MRI) detectable lesions by 56% compared with estrogen supplementation, and the combination of ovariectomy and letrozole further reduced the large lesions to 14.4% compared with control.33 Letrozole is a clinical aromatase inhibitor that blocks the enzyme that produces estrogen, and is used widely for ER+ breast cancer treatment. These important findings provide a therapeutic rationale to use estrogen-depletion therapies to prevent or delay development of BM in younger women, especially letrozole and other aromatase inhibitors with good BBB permeability.17

In addition to astrocytes, microglia, being resident macrophages of the brain, normally exhibit tumor-defensive function by phagocytosis and release of cytotoxic factors. However, the tumor-interacting microglia can be polarized into immunosuppressive and tumor-supportive roles by tumor-derived soluble factors, thereby promoting tumor progression.35 Xing et al., identified a specific long non-coding RNA, X-inactive–specific transcript (XIST) significantly down-regulated in brain metastatic tumors from breast cancer patients and several BCBM cell lines. The researchers concluded that the loss of the XIST promotes BCBM.18 BCBM tumor cells with reduced expression of XIST showed elevated exosomal miRNA-503, which triggered M1–M2 polarization of microglia and augmented release of immune suppressive cytokines in microglia that suppressed T-cell proliferation. The Prestwick FDA-approved drug library was screened on the XISTlow breast tumor cells and fludarabine was identified as a synthetic lethal drug in inhibiting BM. Fludarabine is an FDA-approved chemotherapeutic drug for treatment of chronic lymphocytic leukemia. However, the IC50 for fludarabine on XISTlow BCBM cells was 10-fold lower than the effective dose for leukemic cells. A low-dosing treatment (i.p., once every 2 days, 10 mg/kg) was used in BCBM mouse models, and fludarabine not only significantly delayed onset of BM, but also suppressed growth of tumor cells in the brain without notable toxicity on neuronal cells.18

Research into the modulation of other mechanisms of BM is also emerging. For example, a
recent study by Benbenishty et al. showed that prophylactic administration of CpG-C, a Toll-like receptor 9 (TLR9) agonist, significantly reduced development of BM in mouse models from lung cancer and melanoma.\textsuperscript{19,36} Systemically administered CpG-C can be taken up by brain endothelial cells, astrocytes, and microglia in mice. The CpG-C-activated microglia displayed elevated mRNA expression of apoptosis-inducing and phagocytosis-related genes and phagocytized tumor cells when microglia and tumor cells were physically contacted at early tumor invasion into the brain. Although no breast cancer model was explored in the study, the similar anti-tumor microglia mechanism among breast cancer, lung cancer, and melanoma BM should warrant investigation into the use of CpG-C in BCBM. Other experimental therapeutic strategies, including targeting various steps in metastatic cell colonization and early tumor growth, such as integrin, matrix metallopeptidase (MMP), and VEGF functions, have been reviewed by Achrol et al.,\textsuperscript{37} and promising anti-BM effects were seen in animal models. In addition, intriguing new mechanistic pathways in BCBM are continuously being explored. For example, tumor exosomal CEMIP protein was taken up by brain endothelial and microglial cells, and induced endothelial cell branching and inflammation in promoting BCBM.\textsuperscript{38} Astrocytic sphingosine-1 phosphate receptor 3 (S1P3) upregulated the permeability of blood–tumor barrier (BTB) through secretion of IL-6 and CCL2 and reduced endothelial cell adhesion, thus facilitating extravasation and colonization of brain tumors.

**Figure 1.** Summary of recent translational therapeutic strategies in repositioning known drugs to target BCBM tumorigenic signaling especially the microenvironmental factors. Silibinin, a commercially available nutraceutical reduced BCBM in animal models and a cohort of 18 patients through suppressing STAT3 activation in the STAT3\textsuperscript{+} pro-metastatic As subpopulation.\textsuperscript{14} Meclofenamate, a FDA-approved anti-inflammatory drug inhibited BCBM tumor growth by blocking PCDH7-Cx43 gap junction between Tu and astrocytes.\textsuperscript{15} Edlfosine, a phase II clinical trial drug in treating leukemia with bone marrow transplants inhibited BCBM by suppressing the PCDH7-PLC\textbeta\textsubscript{3} signaling that mediates the crosstalk between astrocytes and brain-tropic CSC.\textsuperscript{16} Letrozole, a clinical aromatase inhibitor for ER\textsuperscript{+} breast cancer treatment, decreased the large BCBM by suppressing ER\textsuperscript{+} pro-metastatic astrocytes.\textsuperscript{17} Fludarabine, a FDA-approved chemotherapeutic drug for treatment of chronic lymphocytic leukemia, inhibited the tumorigenic property of XIST-low and the tumor suppressive M2 microglia that not only delayed onset, but also suppressed growth of BCBM.\textsuperscript{18} CpG-C, a clinical trial TLR9 agonist, prevented BM by activating M1 microglial cells to kill and phagocytose the tumor cells during the early stages of invasion into the brain.\textsuperscript{19} A, astrocyte; BCBM, breast cancer brain metastasis; CSC, cancer stem cells; ER\textsuperscript{+}, estrogen receptor-positive; FDA, United States Food and Drug Administration; TLR9, Toll-like receptor 9; Tu, tumor cells; XIST-low, XIST\textsuperscript{low} tumor cells.
metastatic tumor cells. Genetically, depletion of these molecules not only showed suppression of tumor growth but also had BCNM prevention effects. Despite the lack of available therapeutic agents, these novel scientific findings will drive continued discovery and development of potential therapeutic opportunities to target these mechanisms.

In addition, targeted carrier or drug delivery systems that selectively increase drug penetration through BBB or BTB have been actively pursued for years. This strategy addresses the low and heterogeneous permeability of therapeutic agents to brain disorders including BCNM. Progress in this field has been nicely reviewed by several groups recently.

Targeted therapy and immunotherapy in BCNM

In the past, BCNM patients were excluded from the clinical testing of targeted treatments because their limited life span confounded assessment of drug efficacy on overall survival. However, recent clinical trials have started to elucidate the potential utility of targeted agents, mostly on HER2-positive BCNM patients. In the newly published HER2CLIMB trial, tucatinib, an investigational oral tyrosine kinase inhibitor that is highly selective for HER2 with minimal inhibition of EGFR, was combined with trastuzumab and capecitabine in patients with previously treated HER2-positive BCNM patients from 155 sites across 15 countries. Impressively, the estimated progression-free survival at 1 year was 24.9% in the tucatinib-combination group and 0% in the placebo-combination group, and the risk of disease progression or death was 52% lower in the tucatinib-combination group than in the placebo-combination group. This is the first demonstration of a drug that can prevent or delay disease progression in patients with prior lapatinib exposure. Lapatinib, a small molecule inhibitor of EGFR and HER2, has good penetration across the BBB, but, with limited activity as a single agent for HER2-positive BCNM, it therefore has been used in combination with capecitabine. A meta-analysis of 12 trials with 799 patients revealed the disease control rate of 65.1% for the lapatinib and capecitabine treatment in HER2-positive BCNM. Lapatinib and capecitabine, however, have overlapping gastrointestinal toxicities, limiting clinical dose intensification and efficacy. In a recent phase I study, a new administration regimen was explored, and escalated high-dose lapatinib was well tolerated when given intermittently and sequentially with flat-dose capecitabine, and antitumor activity of such treatment regimen was noted in both CNS and non-CNS sites of disease. In addition, a retrospective study evaluated the addition of concurrent lapatinib to stereotactic radiosurgery (SRS), and concluded with improved complete response rates among patients with HER2-positive BCNM. The antibody drug conjugate trastuzumab-emtansine (T-DM1) is an approved second line treatment for metastatic HER2-positive tumors after trastuzumab. Patients with BMs treated in the phase III EMILIA trial had improved survival with T-DM1 compared with lapatinib plus capecitabine. Intracranial trastuzumab levels can be dramatically increased after radiation therapy, and concomitant T-DM1 with whole brain radiation therapy (WBRT) induced a complete response in a patient with HER2-positive brain and leptomeningeal metastasis. There are several other targeted therapies for BCNM under clinical evaluation, including GDC-0084 in combination with trastuzumab for HER2-positive BCNM [ClinicalTrials.gov identifier: NCT03765983] in which GDC-0084 is a PI3K/Akt/mTOR-pathway inhibitor; everolimus in combination with trastuzumab and vinorelbine for HER2-positive BCNM in which everolimus is a brain-permeable mTOR inhibitor; and ketoconazole in treating patients with recurrent glioma or BCNM in which ketoconazole is an antifungal drug in blocking the function of protein tGLI1 [ClinicalTrials.gov identifier: NCT03796273]. In addition, derivatives of traditional chemotherapy agents could have better CNS penetration and intracranial activity. ANG 1005, which is a modified form of paclitaxel, is one such
molecule showing promising activity in early clinical trials.\textsuperscript{54} Viral vector delivery of agents like trastuzumab is another novel strategy that has promising preclinical data in BCBM prevention and treatment.\textsuperscript{55}

Immunotherapy has activity for BMs from lung cancer and melanoma,\textsuperscript{56–58} but BCBM de have a lower immune content compared with primary tumors, yet improved outcomes are associated with higher TIL content in the BCBM.\textsuperscript{59,60} Thus, strategies were proposed to alter the complex brain immune microenvironment, including concurrent SRS, bi-specific antibody armed activated T cells,\textsuperscript{61} and HER2-chimeric antigen receptor (CAR) T cells in BCBM treatment.\textsuperscript{62} It was hypothesized that SRS treatment would damage BCBM cancer cells and make them more visible to the immune system, and SRS plus atezolizumab (Tecentriq, a PD-L1 antibody), is currently under clinical evaluation in patients with TNBC BM[ClinicalTrials.gov identifier: NCT03483012]. The use of bi-specific antibody activated T cells or HER2-CARTs for BCBM treatment is still under experimental examination. Saul \textit{et al.} showed that HER2-CARs containing the 4-1BB costimulatory domain conferred an improved tumor targeting effect and reduced T-cell exhaustion phenotype. Local intracranial delivery of these HER2-CARs showed potent \textit{in vivo} antitumor activity against multifocal brain and leptomeningeal metastases in orthotopic xenograft models.\textsuperscript{62}

\textbf{Minimally invasive neurosurgery for BCBM}

Surgery is typically reserved for BM patients with solitary and accessible lesions, or symptomatic lesions, good neurologic function, and/or those with good systemic control of the primary tumors. Modern advances in minimally invasive neurosurgical techniques, intraoperative imaging-guided neuronavigation, and brain mapping have allowed for safer resection of BCBM, even within deep or eloquent brain regions. Stereotactic laser ablation or laser interstitial thermal therapy, which involves inserting a small laser catheter through a burr hole, have shown promise for treating inaccessible lesions or those that have undergone radiation necrosis.\textsuperscript{63–67} Similarly, convection-enhanced delivery is a minimally invasive approach using image-guided catheter placement that circumvents the limitations of BBB to potentially enhance drug delivery to BCBM.\textsuperscript{68} In addition, intraoperative fluorescence-guided surgery has been applied to visualize and resect aggressive microscopic tumor margin in BCBM.\textsuperscript{69} The role of neurosurgery in the management of BCBM is evolving rapidly, and is expected to become an increasingly important part of the global management of BCBM patients, whether to alleviate the effects of symptomatic mass lesions, deliver therapy, or mitigate treatment-related toxicity. Another role for surgery stems from the observations that molecular and immunologic profiles of BM are distinct from those of the primary or non-CNS metastatic tumor sites, whereas multi-regional BMs in the same patient are similar.\textsuperscript{70} Therefore, resection or biopsy may have an expanded indication to guide tailored therapy unique to each patient’s BCBM.

\textbf{Clinical radiotherapy}

Whereas surgery and systemic therapies are treatment options for selected BCBM patients, radiotherapy remains the cornerstone of treatment in most patients. Because the side effects of WBRT in cognitive deterioration and quality of life are better understood,\textsuperscript{71} a big shift toward stereotactic radiosurgery (SRS) has occurred over the past decade. The SRS technique relies on multiple radiation beams intersecting at a target localized with three-dimensional image guidance navigation. This results in precise deliver of a high radiation dose with rapid dose fall-off to optimize treatment effects and minimize damage to any adjacent tissue. This is most commonly delivered as a single session (SRS) but can be delivered in up to five fractions (stereotactic radiotherapy to mitigate side effects in larger lesions.

Currently, SRS is an established treatment for patients with \textit{<}4 BMs.\textsuperscript{72} For patients with \textit{\geq}4 BMs, several clinical trials are ongoing, including the Netherlands randomized phase III trial [ClinicalTrials.gov identifier: NCT02353000] in comparing the standard treatment WBRT with SRS is patients with 4–10 BMs, to evaluate the primary endpoint of quality of life at 3 months after radiotherapy\textsuperscript{22}; another randomized phase III trial [ClinicalTrials.gov identifier: NCT01592968] at the MD Anderson Cancer Center for patients with 4–15 BMs compares SRS alone versus WBRT alone. The primary endpoints are cognitive function and local tumor control at 4 months. In addition, a recently registered randomized phase III trial [ClinicalTrials.gov identifier: NCT03550391] compares effects of receiving...
SRS versus hippocampal-avoidant WBRT for patients with 5–15 BMs to establish whether this approach can mitigate the cognitive morbidity associated with WBRT.

Other promising strategies include SRS combined with systemic therapy and novel applications of SRS. For example, lapatinib, which has shown improved complete response rates among patients with HER2-positive BCBM,\(^{48}\) or immunotherapy pembrolizumab (Keytruda) [ClinicalTrials.gov identifier: NCT03449238] and atezolizumab in patients with TNBC BM [ClinicalTrials.gov identifier: NCT03483012]. Individualized isotoxic dose prescription (IDP) has been advocated to mitigate the risk of radionecrosis and further enhance local control probability of SRS.\(^{73-75}\) For large lesions not amenable to single-session treatment, staged SRS has shown promise,\(^{76}\) whereas preliminary studies of re-treated lesions report promising rates of tumor control and side effects.\(^{77-79}\) Finally, new approaches that use metabolic and functional imaging for treatment planning may provide more precise and safe targeting for recurrent treated tumors and those near functional structures such as the corticospinal tracts.\(^{80}\)

**Conclusion**

Treatment options for BCBM continue to increase with exploitation of the molecular characterization.

---

**Table 1.** New clinical trials for BCBM patients.

| Treatment category | Trial description (n) | Trial duration | ClinicalTrials.gov identifier |
|--------------------|-----------------------|----------------|-------------------------------|
| **Systemic therapy** | GDC-0084 plus Trastuzumab | HER2+ BCBM, single-arm, phase II (47) | 12/2018– | NCT03765983 |
| Ketoconazole | BCBM, two arms: Ketoconazole before standard surgery versus standard surgery, phase I (16) | 1/2019– | NCT03796273 |
| Lapatinib plus capecitabine | HER2+ BCBM, two arms: Lapatinib plus capecitabine versus Trastuzumab plus capecitabine, randomized phase III (540) | 04/2009–03/2018 | NCT0082022220 |
| Neratinib | HER2+ BCBM, single-arm, phase II (40) | 12/2011–11/2019 | NCT014946629 |
| Neratinib plus capecitabine | HER2+ BCBM, single-arm, phase II (39) | 12/2011–11/2019 | NCT0149466221 |
| Neratinib plus capecitabine | HER2+ BCBM, two arms: Neratinib plus capecitabine versus Lapatinib plus capecitabine, randomized phase III (621) | 03/2013–12/2019 | NCT01808573 |
| **Radiotherapy** | WBRT versus SRS for 4–10 BM | BM including BCBM, two arms: WBRT versus SRS, randomized [31] | 2/2015– | NCT023530022 |
| | WBRT versus SRS for 4–15 BM | Non-melanoma BM, two arms: WBRT versus SRS, randomized phase III (100) | 08/2012– | NCT01592968 |
| | HA-WBRT plus Memantine | BM including BCBM, two arms: HA-WBRT plus Memantine versus SRS, randomized phase III (206) | 06/2018– | NCT03550391 |
| **Combination therapy** | Pembrolizumab plus SRS | BCBM, single arm, phase I–II (41) | 02/2018– | NCT03449238 |
| | Atezolizumab plus SRS | TNBC BCBM, single arm, phase II (45) | 03/2018– | NCT03483012 |

BCBM, breast cancer brain metastasis; HA-WBRT, hippocampal-avoidant whole brain radiotherapy; SRS, stereotactic radiosurgery; TNBD, triple-negative breast cancer; WBRT, whole brain radiotherapy.
of BCBM tumors and their interactions with the brain microenvironment. The identified repositioned drugs target BCBM tumorigenic signals can be tested in clinical settings in a fast-track way. Advances in minimally invasive neurosurgery and stereotactic radiotherapy also improve the localization of the BM treatment, improving the long-term survival and quality of life of the BCBM patients. In contrast to a one-size-fits-all approach in cancer treatment, with more and more clinical options and different therapeutics strategies becoming available, a multi-disciplinary approach for treatment decision-making is needed in order to best meet individual patient’s needs. Eventually, as prevention of BM has been seen in certain experimental therapeutic strategies in animal studies, preventive clinical studies in high-risk BCBM patients are on the horizon.

Acknowledgments
The authors would like to thank Dorothy Lewis and Rebecca Danforth for proofreading the manuscript.

Conflict of interest statement
The authors declare that there is no conflict of interest.

Funding
The authors disclosed receipt of the following financial support for the research, authorship, and/or publication of this article: This work was funded by National Institutes of Health (NIH) 1R01CA238727 to H.Z and S.T.W, and U54 CA149196, NIH U01CA188388, John S. Dunn Research Foundation, and TT and WF Chao Foundation to S.T.W. PLA Navy NO.905 Hospital Management Project to D.R. Dunn foundation to RCP.

ORCID iD
Hong Zhao https://orcid.org/0000-0001-8991-7824

References
1. Lin NU, Gaspar LE and Soffietti R. Breast cancer in the central nervous system: multidisciplinary considerations and management. Am Soc Clin Oncol Educ Book 2017; 37: 45–56.
2. Mills MN, Figura NB, Arrington JA, et al. Management of brain metastases in breast cancer: a review of current practices and emerging treatments. Breast Cancer Res Treat 2020; 180: 279–300.
3. Pestalozzi BC, Holmes E, de Azambuja E, et al. CNS relapses in patients with HER2-positive early breast cancer who have and have not received adjuvant trastuzumab: a retrospective substudy of the HERA trial (BIG 1-01). Lancet Oncol 2013; 14: 244–248.
4. Mehta AI, Brufsky AM and Sampson JH. Therapeutic approaches for HER2-positive brain metastases: circumventing the blood-brain barrier. Cancer Treat Rev 2013; 39: 261–269.
5. Hochmair M. Medical treatment options for patients with epidermal growth factor receptor mutation-positive non-small cell lung cancer suffering from brain metastases and/or leptomeningeal disease. Target Oncol 2018; 13: 269–285.
6. Martin TA, Lalani AS, Avogadri Connors F, et al. Preclinical characterization of neratinib in a blood-brain barrier co-culture model: therapeutic implications for breast cancers with brain metastases. Cancer Res 2018; 78(Suppl. 4): Abstract P1-17-07.
7. Lin NU. Better treatments needed for breast cancer brain metastases. Lancet Oncol 2015; 16: 1583–1584.
8. Pegram MD. Neratinib in ERBB2-positive brain metastases. JAMA Oncol 2016; 2: 1541–1543.
9. Freedman RA, Gelman RS, Wefel JS, et al. Translational breast cancer research consortium (TBCRC) 022: a phase II trial of neratinib for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. J Clin Oncol 2016; 34: 945–952.
10. Nowak-Sliwinska P, Scapozza L and Ruiz IAA. Drug repurposing in oncology: compounds, pathways, phenotypes and computational approaches for colorectal cancer. Biochim Biophys Acta Rev Cancer 2019; 1871: 434–454.
11. Verbaanderd C, Meheus L, Huys I, et al. Repurposing drugs in oncology: next steps. Trends Cancer 2017; 3: 543–546.
12. Huang L, Garrett Injac S, Cui K, et al. Systems biology-based drug repositioning identifies digoxin as a potential therapy for groups 3 and 4 medulloblastoma. Sci Transl Med 2018; 10: eaat0150.
13. Jin G and Wong ST. Toward better drug repositioning: prioritizing and integrating existing methods into efficient pipelines. Drug Discov Today 2014; 19: 637–644.
14. Priego N, Zhu L, Monteiro C, et al. STAT3 labels a subpopulation of reactive astrocytes required for brain metastasis. Nat Med 2018; 24: 1024–1035.

15. Chen Q, Boire A, Jin X, et al. Carcinoma-astrocyte gap junctions promote breast metastasis by cGAMP transfer. Nature 2016; 533: 493–498.

16. Ren D, Zhu X, Kong R, et al. Targeting brain-adaptive cancer stem cells inhibits brain metastatic colonization of triple-negative breast cancer. Cancer Res 2018; 78: 2052–2064.

17. Dave N, Gudelsky GA and Desai PB. The pharmacokinetics of letrozole in brain and brain tumor in rats with orthotopically implanted C6 glioma, assessed using intracerebral microdialysis. Cancer Chemother Pharmacol 2013; 72: 349–357.

18. Xing F, Liu Y, Wu SY, et al. Loss of XIST in breast cancer activates MSN-c-Met and reprograms microglia via exosomal miRNA to promote breast metastasis. Cancer Res 2018; 78: 4316–4330.

19. Baratta MG. Better safe than sorry: a potential prophylactic treatment for breast metastasis. Nat Rev Cancer 2019; 19: 303.

20. Pivot X, Manikhas A, Zurawski B, et al. CEREBEL (EGF111438): a phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. J Clin Oncol 2015; 33: 1564–1573.

21. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: a phase II Trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. J Clin Oncol 2019; 37: 1081–1089.

22. Zindler JD, Bruynzeel AME, Eekers DPB, et al. Whole brain radiotherapy versus stereotactic radiosurgery for 4-10 brain metastases: a phase III randomised multicentre trial. BMC Cancer 2017; 17: 500.

23. Valiente M, Obenauf AC, Jin X, et al. Serpins promote cancer cell survival and vascular co-option in brain metastasis. Cell 2014; 156: 1002–1016.

24. Nguyen DX, Chiang AC, Zhang XH, et al. WNT/TCF signaling through LEF1 and HOX8 mediates lung adenocarcinoma metastasis. Cell 2009; 138: 51–62.

25. Lorger M and Felding-Habermann B. Capturing changes in the brain microenvironment during initial steps of breast cancer brain metastasis. Am J Pathol 2010; 176: 2958–2971.

26. Fitzgerald DP, Palmieri D, Hua E, et al. Reactive glia are recruited by highly proliferative brain metastases of breast cancer and promote tumor cell colonization. Clin Exp Metastasis 2008; 25: 799–810.

27. Kim SJ, Kim JS, Park ES, et al. Astrocytes upregulate survival genes in tumor cells and induce protection from chemotherapy. Neoplasia 2011; 13: 286–298.

28. Zhang L, Zhang S, Yao J, et al. Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth. Nature 2015; 527: 100–104.

29. Roderick HL and Cook SJ. Ca2+ signalling checkpoints in cancer: remodelling Ca2+ for cancer cell proliferation and survival. Nat Rev Cancer 2008; 8: 361–375.

30. Wu J, Sun L, Chen X, et al. Cyclic GMP-AMP is an endogenous second messenger in innate immune signaling by cytosolic DNA. Science 2013; 339: 826–830.

31. Kim SY, Chung HS, Sun W, et al. Spatiotemporal expression pattern of non-clustered protocadherin family members in the developing rat brain. Neuroscience 2007; 147: 996–1021.

32. Xiao H, Sun Z, Wan J, et al. Overexpression of protocadherin 7 inhibits neuronal survival by downregulating BIRC5 in vitro. Exp Cell Res 2018; 366: 71–80.

33. Sartorius CA, Hanna CT, Gril B, et al. Estrogen promotes the brain metastatic colonization of triple negative breast cancer cells via an astrocyte-mediated paracrine mechanism. Oncogene 2016; 35: 2881–2892.

34. Contreras-Zarate MJ, Day NL, Ormond DR, et al. Estradiol induces BDNF/TrkB signaling in triple-negative breast cancer to promote brain metastases. Oncogene 2019; 38: 4685–4699.

35. Wu SY and Watabe K. The roles of microglia/macrophages in tumor progression of breast cancer and metastatic disease. Front Biosci (Landmark Ed) 2017; 22: 1805–1829.

36. Benbenishty A, Gadrich M, Cottarelli A, et al. Prophylactic TLR9 stimulation reduces brain metastasis through microglia activation. PLoS Biol 2019; 17: e2006859.

37. Boire A, Brastianos PK, Garzia L, et al. Brain metastasis. Nat Rev Cancer 2020; 20: 4–11.

38. Rodrigues G, Hoshino A, Kenific CM, et al. Tumour exosomal CEMIP protein promotes cancer cell colonization in brain metastasis. Nat Cell Biol 2019; 21: 1403–1412.
39. Gril B, Paranjape AN, Woditschka S, et al. Reactive astrocytic S1P3 signaling modulates the blood-tumor barrier in brain metastases. *Nat Commun* 2018; 9: 2705.
40. Mendes M, Sousa JJ, Pais A, et al. Targeted theranostic nanoparticles for brain tumor treatment. *Pharmaceutics* 2018; 10: 181.
41. Chaudhuri TR and Straubinger RM. Nanotechnology meets oncology: nanomaterials in brain cancer research, diagnosis and therapy. *Nanomaterials* 2019; 9: 1285.
42. Zottel A, Videtic Paska A and Jovcevska I. Nanotechnology meets oncology: nanoparticles for brain tumor delivery. In: Lonser RR, Sarntinoranont M and Bankiewicz K (eds) *Nervous System Drug Delivery Principles and Practice*. Academic Press, 2019, pp. 229–250.
43. Murphy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J Med* 2020; 382: 597–609.
44. Bradley CA. Brain metastases respond to neratinib plus capecitabine. *Nat Rev Clin Oncol* 2019; 16: 336.
45. Cihan YB. Lapatinib? or radiotherapy? In cranial metastasis of breast cancer. *Eur J Breast Health* 2019; 15: 205–206.
46. Petrelli F, Ghidini M, Lonati V, et al. The efficacy of lapatinib and capecitabine in HER-2 positive breast cancer with brain metastases: a systematic review and pooled analysis. *Eur J Cancer* 2017; 84: 141–148.
47. Morikawa A, de Stanchina E, Pentsova E, et al. Phase I study of intermittent high-dose lapatinib alternating with capecitabine for HER2-positive breast cancer patients with central nervous system metastases. *Clin Cancer Res* 2019; 25: 3784–3792.
48. Kim JM, Miller JA, Kotecha R, et al. Stereotactic radiosurgery with concurrent HER2-directed therapy is associated with improved objective response for breast cancer brain metastasis. *Neuro Oncol* 2019; 21: 659–668.
49. Krop IE, Lin NU, Blackwell K, et al. Trastuzumab emtansine (T-DM1) versus lapatinib plus capecitabine in patients with HER2-positive metastatic breast cancer and central nervous system metastases: a retrospective, exploratory analysis in EMILIA. *Ann Oncol* 2015; 26: 113–119.
50. Dieras V, Miles D, Verma S, et al. Trastuzumab emtansine versus capecitabine plus lapatinib in patients with previously treated HER2-positive advanced breast cancer (EMILIA): a descriptive analysis of final overall survival results from a randomised, open-label, phase 3 trial. *Lancet Oncol* 2017; 18: 732–742.
51. Venur VA, Cohen JV and Brastianos PK. Targeting molecular pathways in intracranial metastatic disease. *Front Oncol* 2019; 9: 99.
52. Ricciardi GRR, Russo A, Franchina T, et al. Efficacy of T-DM1 for leptomeningeal and brain metastases in a HER2 positive metastatic breast cancer patient: new directions for systemic therapy - a case report and literature review. *BMC Cancer* 2018; 18: 97.
53. Van Swaeringen AED, Siegel MB, Deal AM, et al. LCCC 1025: a phase II study of everolimus, trastuzumab, and vinorelbine to treat progressive HER2-positive breast cancer brain metastases. *Breast Cancer Res Treat* 2018; 171: 637–648.
54. Kumthekar P, Tang SC, Brenner AJ, et al. ANG1005, a brain penetrating peptide-drug conjugate, shows activity in patients with breast cancer with leptomeningeal carcinomatosis and recurrent brain metastases. *Clin Cancer Res*. Epub ahead of print 22 January 2020. DOI: 10.1158/1078-0432.CCR-19-3258.
55. Rothwell WT, Bell P, Richman LK, et al. Intrathecal viral vector delivery of trastuzumab prevents or inhibits tumor growth of human HER2-positive xenografts in mice. *Cancer Res* 2018; 78: 6171–6182.
56. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med* 2018; 379: 722–730.
57. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol* 2016; 17: 976–983.
58. Kluger HM, Chiang V, Mahajan A, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. *J Clin Oncol* 2019; 37: 52–60.
59. Ogiba R, Niikura N, Kumaki N, et al. Comparison of immune microenvironments between primary tumors and brain metastases in patients with breast cancer. *Oncotarget* 2017; 8: 103671–103681.
60. Sambade MJ, Prince G, Deal AM, et al. Examination and prognostic implications of the unique microenvironment of breast cancer brain metastases. *Breast Cancer Res Treat* 2019; 176: 321–328.
61. Dahlen E, Veitoknami N and Norlen P. Bispecific antibodies in cancer immunotherapy. *Ther Adv Vaccines Immunother* 2018; 6: 3–17.

62. Priceman SJ, Tilakawardane D, Jeang B, et al. Regional delivery of chimeric antigen receptor-engineered T cells effectively targets HER2+ breast cancer metastasis to the brain. *Clin Cancer Res* 2018; 24: 95–105.

63. Marenco-Hillembrand L, Alvarado-Estrada K and Chaichana KL. Contemporary surgical management of deep-seated metastatic brain tumors using minimally invasive approaches. *Front Oncol* 2018; 8: 558.

64. Gassie K, Alvarado-Estrada K, Bechtle P, et al. Surgical management of deep-seated metastatic brain tumors using minimally invasive approaches. *J Neurol Surg A Cent Eur Neurosurg* 2019; 80: 198–204.

65. Ahluwalia M, Barnett GH, Deng D, et al. Laser ablation after stereotactic radiosurgery: a multicenter prospective study in patients with metastatic brain tumors and radiation necrosis. *J Neurosurg* 2018; 130: 804–811.

66. Rennert RC, Khan U, Tatter SB, et al. Patterns of clinical use of stereotactic laser ablation: analysis of a multicenter prospective registry. *World Neurosurg* 2018; 116: e566–e570.

67. Beechar VB, Prabhu SS, Bastos D, et al. Volumetric response of progressing post-SRS lesions treated with laser interstitial thermal therapy. *J Neurooncol* 2018; 137: 57–65.

68. Stine CA and Munson JM. Convection-enhanced delivery: connection to and impact of interstitial fluid flow. *Front Oncol* 2019; 9: 966.

69. Hardesty DA and Nakaji P. The current and future treatment of brain metastases. *Front Surg* 2016; 3: 30.

70. Leibold AT, Monaco GN and Dey M. The role of the immune system in brain metastasis. *Curr Neurobiol* 2019; 10: 33–48.

71. Brown PD, Ahluwalia MS, Khan OH, et al. Whole-brain radiotherapy for brain metastases: evolution or revolution? *J Clin Oncol* 2018; 36: 483–491.

72. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* 2016; 316: 401–409.

73. Zindler JD, Thomas CR Jr, Hahn SM, et al. Increasing the therapeutic ratio of stereotactic ablative radiotherapy by individualized isotonic dose prescription. *J Natl Cancer Inst* 2016; 108: djv305.

74. O’Beirn M, Benghiat H, Meade S, et al. The expanding role of radiosurgery for brain metastases. *Medicines (Basel)* 2018; 5: 90.

75. Hartgerink D, van der Heijden B, De Ruyscher D, et al. Stereotactic radiosurgery in the management of patients with brain metastases of non-small cell lung cancer: indications, decision tools and future directions. *Front Oncol* 2018; 8: 154.

76. Angelov L, Mohammadi AM, Bennett EE, et al. Impact of 2-staged stereotactic radiosurgery for treatment of brain metastases ≥ 2 cm. *J Neurosurg* 2018; 129: 366–382.

77. Balarampa S, Stera S, Muller von der Grun J, et al. Repeated in-field radiosurgery for locally recurrent brain metastases: feasibility, results and survival in a heavily treated patient cohort. *PLoS One* 2018; 13: e0195608.

78. Huang Z, Sun B, Shen G, et al. Brain metastasis reirradiation in patients with advanced breast cancer. *J Radiat Res* 2017; 58: 142–148.

79. Moreau J, Khalil T, Dupic G, et al. Second course of stereotactic radiosurgery for locally recurrent brain metastases: safety and efficacy. *PLoS One* 2018; 13: e0195608.

80. Scranton RA, Sadrameli S, Butler EB, et al. Coregistration of magnetic resonance and [18F] fludeoxyglucose-positron emission tomography imaging for stereotactic radiation therapy planning: case report in a previously irradiated brain metastasis with recurrent tumor and radiation necrosis. *Pract Radiat Oncol* 2020; 10: 133–137.