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Chemical compounds studied in this article:
5-azacitidine (PubMED CID: 9444)
5-fluorouracil (PubMED CID: 3385)
Afatinib (PubMED CID: 10184653)
Abemaciclib (PubMED CID: 46220502)
Alisertib (PubMED CID: 24471867)
Alpelisib (PubMED CID: 56649450)
Anastrozole (PubMED CID: 2187)
Apitolisib (PubMED CID: 25254071)
Bleomycin (PubMED CID: 5360373)
Brilanestrant (PubMED CID: 56941241)
Buparlisib (PubMED CID: 16654980)
Cabozantinib (PubMED CID: 25102847)
Capecitabine (PubMED CID: 60953)
Carmustine (PubMED CID: 2578)
Cisplatin (PubMED CID: 84691)
Cyclophosphamide (PubMED CID: 2907)
Cytarabine (PubMED CID: 6253)
Dactolisib (PubMED CID: 11977753)
Daunorubicin (PubMED CID: 30323)
Docetaxel (PubMED CID: 148124)
Doxorubicin (PubMED CID: 31703)
Elacestrant (PubMED CID: 23462301)
Entinostat (PubMED CID: 4261)
Eribulin (PubMED CID: 17755248)
Estradiol (PubMED CID: 5757)
Etirinotecan pegol (PubMED CID: 71300725)
Etoposide (PubMED CID: 36462)
Everolimus (PubMED CID: 18477728)
Exemestane (PubMED CID: 60198)
Fulvestrant (PubMED CID: 104741)
Gemcitabine (PubMED CID: 60750)
Goserelin (PubMED CID: 5311128)
Ifosfamide (PubMED CID: 3690)
Iniparib (PubMED CID: 9796068)
Irinotecan (PubMED CID: 60838)
Lapatinib (PubMED CID: 208908)
Lenvatinib (PubMED CID: 9823820)
Letrozole (PubMED CID: 3902)
Leuprorelin (PubMED CID: 657181)
Lomustine (PubMED CID: 3950)
Methotrexate (PubMED CID: 126941)
Mitoxantrone (PubMED CID: 4212)
Neratinib (PubMED CID: 9915743)
Olaparib (PubMED CID: 23725625)
Palbociclib (PubMED CID: 122706004)
Paclitaxel (PubMED CID: 36314)
Pictilisib (PubMED CID: 17755052)
Pilaralisib (PubMED CID: 56599306)
Ribociclib (PubMED CID: 44631912)
Rucaparib (PubMED CID: 9931954)
Sonidegib (PubMED CID: 24775005)
Sunitinib (PubMED CID: 5329102)
Tamoxifen (PubMED CID: 2733526)

Investigational chemotherapy and novel pharmacokinetic mechanisms for the treatment of breast cancer brain metastases

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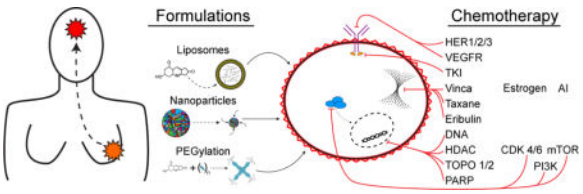
Abstract

In women, breast cancer is the most common cancer diagnosis and second most common cause of cancer death. More than half of breast cancer patients will develop metastases to the bone, liver, lung, or brain. Breast cancer brain metastases (BCBM) confers a poor prognosis, as current therapeutic options of surgery, radiation, and chemotherapy rarely significantly extend life and are considered palliative. Within the realm of chemotherapy, the last decade has seen an explosion of novel chemotherapeutics involving targeting agents and unique dosage forms. We provide a historical overview of BCBM chemotherapy, review the mechanisms of new agents such as poly-ADP ribose polymerase inhibitors, cyclin-dependent kinase 4/6 inhibitors, phosphatidyl inositol 3-kinaseinhibitors, estrogen pathway antagonists for hormone-receptor positive BCBM; tyrosine kinase inhibitors, antibodies, and conjugates for $HER2^+$ BCBM; repurposed cytotoxic chemotherapy for triple negative BCBM; and the utilization of these new agents and formulations in ongoing clinical trials. The mechanisms of novel dosage formulations such as nanoparticles, liposomes, pegylation, the concepts of enhanced permeation and retention, and drugs utilizing these concepts involved in clinical trials are also discussed. These new treatments provide a promising outlook in the treatment of BCBM.

Graphical abstract



Taselisib (PubMED CID: 51001932)
Temozolomide (PubMED CID: 5394)
Teniposide (PubMED CID: 452548)
Topotecan (PubMED CID: 60700)
Tucatinib (PubMED CID: 51039094)
Veliparib (PubMED CID: 11960529)
Vincristine (PubMED CID: 5978)
Vinorelbine (PubMED CID: 5311497)
Voxtalisib (PubMED CID: 49867926)
Z-endoxifen (PubMED CID: 10090750)

Declarations of Interest: none.

Keywords

breast cancer brain metastases; novel chemotherapy; nanoparticles; liposomes; pegylation; clinical trials

1. EPIDEMIOLOGY

Second only to heart disease, cancer accounted for 23% of recorded deaths in 2014. In women, lung cancer is the leading cause of cancer death, followed by breast cancer, and then colorectal cancer. It is estimated in 2018 there will be more than 260,000 new cases of breast cancer and more than 40,000 deaths as a result of the disease [1]. Breast cancer is one of the most common cancer diagnoses in women, with a 1-in-8 total lifetime risk for diagnosis [2]. Though breast cancer may be diagnosed at any age, a recently published report placed the average age of diagnosis at 50 years old [3]. This report also found that in those cases in which information on ethnicity was available, 68% were Caucasian, 17% were African American, and 11% were Hispanic.

Although not as common in men, breast cancer incidence within this population is increasing. The incidence in men is typically associated with factors such as a high body mass index, Klinefelter syndrome, gynecomastia, liver disease, testicular disease, alcoholism, and radiation exposure. Male breast cancer is most comparable to breast cancer that presents in postmenopausal women, but with a few distinct differences. In men, breast cancer is typically discovered at an older age and presents at a more advanced stage. In addition, male breast cancer has higher rates of estrogen and progesterone receptor positivity than female breast cancer. There is also evidence that genetic predisposition plays a larger role in developing breast cancer in males [4].

One of the biggest challenges of treating breast cancer is its propensity to metastasize to other areas of the body, including liver, bone, lung, and brain. After lung cancer, breast cancer is the second most common source of brain metastases [5] (Figure 1). Of patients diagnosed with breast cancer, between 10–15% will develop brain metastases [6] with the median time of presentation 2-3 years after initial diagnosis [7]. In about 30% of breast cancer patients, metastatic lesions in the brain were found *post-mortem* [8–11]. Brain metastases of breast cancer are associated with limited survival and a lower quality of life.

Some risk factors that have been associated with the development of brain metastases in women include: diagnosis of breast cancer at a younger age, tumors that are large or high grade, presence of lymph node metastases, and certain subtypes of breast cancer. The subtypes that have been shown to preferentially metastasize to the brain include estrogen-receptor negative, estrogen, progesterone, and HER2 receptor negative (triple negative), and $HER2^{+}$ breast cancers [3]. Survival for patients that have developed brain metastases is low, ranging from 2 to 16 months after diagnosis.

Current treatment strategies for breast cancer brain metastases (BCBM) include surgery, whole brain radiation or stereotactic radiosurgery, chemotherapy, and biological therapy [3]. Although these methods increase survival, the prognosis for patients with metastatic breast

cancer, especially those with brain metastases, remains poor. The treatment of brain metastases is especially challenging due to the number and location of secondary tumors, performance status of the patient, and the biological subtype of the primary breast cancer [12]. Many chemotherapeutic agents commonly used to treat primary breast cancer are unable to penetrate the blood-brain barrier (BBB), which is a highly selective cellular barrier that acts as a gatekeeper for solutes to enter the brain. In addition to keeping unwanted physiologic substances out of the brain, it also prevents many chemotherapeutic agents from reaching therapeutic concentrations within the brain, leading to potential resistance [13].

The incidence of brain metastases of breast cancer is increasing. Since 1979, the frequency of stage IV breast cancer has increased from 10% in 1979 to 24%. [3]. Today, more brain metastases are detected and diagnosed due to advanced imaging techniques. Although more advanced and efficacious therapies are allowing patients to live longer, the increase in survival has also increased the probability that primary cancer will metastasize to the brain [3]. The increasing rate of brain metastases necessitates the development of novel treatment strategies, which will be highlighted in this review.

2. Physiology / Pathology

2.1 Blood-Brain Barrier

Blood vessels, which deliver blood from the heart to different organs, have different properties to meet the requirements of the particular organ or tissue they vascularize [14]. Neurons of the brain communicate by chemical and electrical signals, which give rise to their function. For these signals to be reliable and reproducible, the ionic concentration of the tissue has to be constant to maintain homeostasis [15]. The microvasculature of the brain plays an important role in regulating the entry of any solute into the brain parenchyma and undisrupted function is required to maintain homoeostasis for proper neuronal function [15]. This unique property of brain microvasculature is described as the blood-brain barrier (Figure 2A). Continuous, non-fenestrated capillaries form the BBB, in which endothelial cells are attached together by tight junction protein complexes including claudins, occludins, and intercellular adhesion molecules. These junctional components restrict the paracellular diffusion of solutes [16, 17]. The brain endothelial cells also restrict vesicle mediated transcellular movement more so than endothelial cells in the periphery [18]. Surrounded by pericytes on the abluminal side, these cells have contractile proteins that regulate the diameter of the capillary [19]. Astrocytic foot processes also cover microvasculature, providing a link between neurons and blood vessels. Through this cellular link, astrocytes mediate blood flow in accordance with neuronal activity [20, 21]. Astrocytes play an important role in the formation of the BBB, and factors secreted by astrocytes play an important role in BBB function [22]. In addition to the physical barrier properties of brain capillaries, a great number of chemical barriers also exist in the BBB. Efflux transporters including p-glycoprotein, the breast cancer resistance protein, and the family of multi-drug resistance proteins are expressed on brain endothelium, which limit lipophilic solutes form entering the brain [23, 24]. Enzymes secreted by the BBB (e.g., phosphatases) inactivate larger molecules including peptides and neuropeptides, preventing their passing through the BBB [25, 26].

2.2 Functions of BBB

The BBB provides a stable and partially sequestered environment for neuronal activity by means of ion regulation. Ion concentrations are kept relatively constant despite the changes in plasma ion concentration due to acute or chronic changes in conditions [27–29]. The BBB also separates central neurotransmitters from peripheral neurotransmitters. For example, the peripheral neuroexcitatory amino acid glutamate is present at high concentrations in peripheral blood and would cause permanent neurotoxic damage if allowed to enter the brain [30]. Macromolecules like albumin, pro-thrombin, and plasminogen may initiate apoptosis and are detrimental to central nervous system, but are restricted by the BBB [31, 32]. Aside from restricting potentially toxic substances, the BBB also plays an important role in regulating nutrition to the brain. Specific transport systems are in place for essential water-soluble nutrients [30]. Many pathways regulate angiogenesis and vasculogenesis, including vascular endothelial growth factor (VEGF) and its receptors (VEGFR). Notch signaling also plays an important role in regulating endothelial cell functions [33, 34].

While the BBB helps maintain homeostasis to support proper brain function, it also restricts delivery of many drugs, including chemotherapy, to the central nervous system (CNS) [35]. Agents such as paclitaxel and doxorubicin are significantly subjected to efflux transport mechanisms present at the BBB [36, 37], prompting development of analogues that can circumvent the BBB and enter brain tissue [38].

2.3 Blood-Tumor Barrier

Once metastatic lesions begin to develop in the brain, BBB integrity is lost and the resulting tumor microvasculature is often referred to as the blood-tumor-barrier (BTB) (Figure 2B) [13]. As metastases grow, they promote the growth of new blood vessels via angiogenesis. These new blood vessels lack tight junctions and proper astrocytic contact. As a result the BTB has increased permeability and reduced blood flow [39–41]. In addition, the angiogenic vessels have fenestrations, which increase permeability through paracellular pathways [42, 43], allowing normally regulated substances to freely enter the tumor and its microenvironment.

However, BTB permeability is not homogenous from tumor to tumor or even within the metastatic lesion [44]. Significant heterogeneity exists within and between tumors based on findings from preclinical breast cancer brain metastases models [13, 45]. Brain metastases become hypoxic as they grow beyond their blood supply. To meet their oxygen and nutrition requirements, tumor cells secrete vascular endothelial growth factor (VEGF) to initiate the process of new blood vessel formation [46]. VEGF secretion is associated with increased turnover of endothelial cells leading to increased permeability [46]. Angiogenesis is a dynamic process, to which the heterogeneity of BTB permeability between tumors can be attributed [47, 48].

A multitude of factors exist that make treatment of BCBM difficult. These factors can be anatomical or tumor-related. The region around the tumor, called the tumor microenvironment, has physiological conditions that vary from the normal tissue physiology. One such difference is hypoxia. Hypoxia induces resistance to drug and radiation therapy

[49]. A few conventional chemotherapy drugs such as bleomycin, etoposide, and cyclophosphamide, require oxygen to exert their cytotoxic effects [50]. Thus, under hypoxic conditions, these drugs fail to have an optimal cytotoxic effect leading to tumor resistance.

2.4 Effects of the BBB and BTB on drug therapy

Although lipophilic drugs have higher tendency to cross the BBB, many drugs achieving this feat are subject to efflux by the efflux pumps of the BBB. The primary efflux transporters belong to the ATP-binding cassette transporter family. Found on the luminal side of the BBB, these include the P-glycoprotein (P-gp), breast cancer resistance protein, and the multi-drug resistance protein [51]. Amongst them, the P-gp, present on both luminal and abluminal side, serves to remove a wide variety of substrates including chemotherapeutic drugs such as paclitaxel. The breast cancer resistance protein efflux transporter is also an important contributing factor in chemotherapy resistance. The BBB is dynamic in nature, and changes are seen in its integrity in different disease states, including metastatic cancer [52]. As stated previously the BTB has a higher permeability to chemotherapy as compared to the intact BBB; however therapeutic concentrations of drug are still unable to get across to the desired site. To add to the challenge, the BTB is highly variable in nature, which leads to variable drug concentrations reaching the target [53]. Chemotherapeutic drugs paclitaxel and doxorubicin were found to penetrate the BTB more easily compared to BBB in a brain metastatic mouse model of breast cancer; however, the drug concentrations in tumor were sub-therapeutic and non-uniform [13, 54]. Circumventing the BBB, BTB, and the efflux processes remain the ultimate challenge for the effective therapy of brain metastases.

3. Subsets of Breast Cancer Brain Metastases

3.1 Hormone receptor-positive

Hormone receptor-positive (HR^+) breast cancer is a subtype of breast cancer that expresses estrogen receptors (ER), progesterone receptors (PR), and human epidermal growth factor receptor 2 (HER2). These types of tumors respond differently to treatment and confer a variety of prognoses [55]. Although PR are typically regulated by ER, they can act independently at times, creating the three types of HR+ BC: ER positive/PR positive, ER positive/PR negative, and ER negative/PR positive [55–57]. ER^+/PR^+ and ER^+/PR^- are more common and generally easier to treat than ER^-/PR^+ due to the presence of ER, which is the target for most HR^+ BC therapies [55]. Furthermore, ER^-/PR^+ BC displays greater growth rates and are less responsive to endocrine therapy related to metastatic BC [56, 57]. The estrogen and progesterone signaling pathways are very similar representations of the typical steroid mechanism [55]. Although there are different types of ER and PR in cells, the main targets of medication are the nuclear transcription factors (i.e. ERα) responsible for cellular growth and proliferation [55, 57]. The endogenous hormones freely diffuse through the cell membrane to their respective protein receptors, which dimerize upon binding their hormone and translocate into the nucleus to bind DNA and activate transcription [55]. The HR^+ BC subtypes tend to be more treatable than other BC subtypes due to the significant effectiveness of endocrine therapy on ER+BC [55].

3.2 Hormone Positive Therapy

There are no chemotherapeutic agents or regimens specifically approved for hormone receptor-positive BCBM, however many are being investigated through clinical trials [58]. Multiple studies have demonstrated that the luminal subtypes of breast cancer (luminal A and luminal B) are associated with decreased likelihood of brain metastasis [59–61]. However, some chemotherapeutic research is being done for the rare cases when hormone receptor positive breast cancer does metastasize to the brain. In 1991, Lien et al. determined tamoxifen and its metabolites achieved 46 times higher concentrations in brain tissue compared to serum levels [62]. Then in 2006, a phase I trial was conducted with 24 BCBM patients receiving a combination of capecitabine and temozolomide [63]. The study reported one complete response and three partial responses warranting the need for further research regarding this therapy [63]. Three years later a retrospective study examined five BCBM patients who were treated concurrently with capecitabine and WBRT [64]. Of the five, one achieved a complete response, two achieved partial responses, one had stable disease, and one patient was deceased [64]. Three years after the previous study, Addeo et al. conducted a trial with the combination of vinorelbine, temozolomide, and WBRT in 36 patients [65]. This study reported three complete and 16 partial responses, with a PFS and OS of eight and 11 months, respectively [65]. After another three-year period, eribulin was compared to capecitabine in the treatment of HR^+ MBC with metastasis to the brain. All three selected patients from the study who received eribulin displayed brain lesion shrinkage during the study and fewer total patients developed new BCBM with eribulin than with capecitabine [66]. This study notes that eribulin does not cross a healthy BBB but capecitabine may [66]. That same year, Niravath *et al.* concluded that concomitant treatment of capecitabine and WBRT followed by capecitabine and sunitinib did not extend PFS and was associated with significant toxicity [67]. Furthermore, in 2015, a prospective study comparing BCBM versus serum concentrations for capecitabine and lapatinib concluded that both drugs penetrate BCBM to a significant albeit variable degree [68]. The American Society of Clinical Oncology recommends endocrine therapy as the initial treatment for HR^+ metastatic breast cancer, with aromatase inhibitors being the first-line [69]. Fulvestrant or human epidermal growth factor receptor 2 (HER2)-targeted therapies can be added to the first-line treatment if the patient has not had prior exposure to adjuvant endocrine therapy or has HR^+ and $HER2^+$ metastatic BC, but it is not recommended to combine targeted endocrine therapy and nonspecific chemotherapy [69]. Table 1 lists the results of clinical trials involving HR^+ BCBM.

3.3 Novel Therapy for Hormone Positive Brain Metastases

There are only a few clinical trials specifically involving HR^+ BCBM. The majority of trials allow for participant enrollment if patients have been previously treated with radiation, surgery, or previous chemotherapy at least 2 weeks to 3 months prior to enrollment, with image-confirmed non-progression of brain lesions, and stability of disease without corticosteroid or anti-epileptic use. A compilation of ongoing and initiated clinical trials for HR^+ BCBM is provided in Table 3. An illustration of overall mechanisms is provided in Figure 3.

3.3.1 CDK4/6 inhibitors—Three cyclin-dependent kinase CDK-4 and -6 (CDK 4/6) inhibitors are being evaluated for their effects in treating hormone-positive BCBM: abemaciclib, palbociclib, and ribociclib. Abemaciclib has proved to be a safe and effective treatment for $HR^+/HER2^-$ metastatic breast cancer in three separate MONARCH trials, the second of which earned the drug approval from the FDA [70–73]. However, women with CNS metastases were excluded from all three trials, raising the question of abemaciclib's efficacy for the treatment of BCBM. Subsequently, there are a few ongoing trials of abemaciclib that include patients with HR^+ BCBM. The first is a Phase II study specifically looking at abemaciclib's safety and effectiveness in participants with BM from non-small cell lung cancer, melanoma, and HR+ BC (NCT02308020). The monarcHER trial is a Phase II study evaluating the effectiveness of abemaciclib and trastuzumab with/without fulvestrant in the BCBM setting (NCT02675231). Lastly, there is an expanded access study for HR+/HER2− metastatic BC to be treated by abemaciclib after disease progression on prior therapies (NCT02792725).

Palbociclib is another CDK4/6-specific inhibitor under investigation in combination with other agents for the treatment of BCBM. It is being explored as monotherapy in the Phase III PATINA study including HR+ BCBM patients (NCT02947685). Palbociclib is also being studied in combination with aromatase inhibitors such as letrozole (NCT02600923), selective estrogen receptor modulators such as bazedoxifene and tamoxifen (NCT02448771, NCT02668666), and selective estrogen receptor degraders such as fulvestrant (NCT02738866). Other combinations with palbociclib include everolimus and exemustane (NCT02871791), exemustane and leuprolide (NCT02592746), fulvestrant or tamoxifen (NCT02384239), and the PI3K inhibitors taselisib or pictilisib (NCT02389842). In the PALINA trial, the combination of palbociclib and either letrozole or fulvestrant is being investigated in treating stable $HR^+/HER2^-$ BCBM participants that self-identify as black, African, or African-American [NCT02692755).

Ribociclib (LEE011) is being explored in combination with many estrogenic pathway inhibitors in the treatment of BCBM. A phase 3 trial is looking at ribociclib efficacy in combination with letrozole (NCT03096847). A Phase 1 trial is evaluating ribociclib and letrozole along with alepelsib (NCT01872260). Similar to the phase 3 MONALEESA-3 trial, ribociclib is combined with fulvestrant for $HR^+/HER2^-$ BCBM (NCT02422615) or following disease progression on prior treatment with an aromatase inhibitor or other CDK 4/6 inhibitor (NCT02632045). In the Phase 1 TEEL study, ribociclib is combined with tamoxifen with and without goserelin in $HR^+/HER2^-$ metastatic breast cancer patients who may also have brain metastases (NCT02586675).

3.3.2 PI3K inhibitors—Three phosphoinositide 3-kinase (PI3K) inhibitors are being evaluated in combination with anti-estrogenic agents for their efficacy in treating hormone-positive BCBM: alpelisib, buparlisib, and dactolisib. In the SOLAR-1 Phase 3 trial, the PI3K inhibitor alpelisib (BYL719) is coadministered with fulvestrant for participants with aromatase inhibitor-refractory HR+/HER2− BCBM (NCT02437318). Similarly, alpelisib is being explored in combination with letrozole for participants with HR+/HER2− non-symptomatic BCBM in a Phase I study (NCT01791478).

In the BELLE-4 study, buparlisib was paired with paclitaxel in the treatment of asymptomatic HER2− metastatic BCBM. Though overall results were posted for 338 patients, no specific results were posted for BM patients (NCT01572727). This trial was meant to be a Phase II study followed by a Phase III, but was ended after the second phase due to pre-defined futility criteria as there was no improvement in progression free survival [74]. Subsequently, buparlisib was paired with fulvestrant in two separate Phase 3 studies, BELLE-2 and BELLE-3, evaluating its effectiveness in treating asymptomatic $HR^+/HER2^-$ BCBM after disease progression on an aromatase inhibitor (BELLE-2) or an mTOR inhibitor (BELLE-3) (NCT01610284, NCT01633060). In a second experimental group of the Phase I B-YOND study, the PI3K inhibitor buparlisib will be combined with tamoxifen and goserelin (NCT02058381). Although no results have been posted, buparlisib completed a Phase I study in combination with letrozole in which BCBM patients were included (NCT01248494). In the Phase II STAR Cape study, buparlisib will be combined with capecitabine to treat any type of BCBM, though the HER2+ subset is also receiving trastuzumab (NCT02000882).

In a second experimental group from a previously mentioned completed phase 1 study, dactolisib will be combined with letrozole for BCBM participants (NCT01248494).

3.3.3 HDAC inhibitor—In a completed phase 1 study, entinostat (SNDX-275) was combined with erlotinib and exemestane for patients with HR^+ metastatic BC including their brain metastases, but no results are posted (NCT01594398). Entinostat is being combined with exemestane in an upcoming Phase 1 trial for patients with similar criteria (NCT02833155).

3.3.4 mTOR inhibitors—In two ongoing Phase 1 trials, everolimus is being explored in combination with letrozole and trastuzumab for HR^+ BCBM patients (NCT02152943, NCT02269670). In a Phase 2 study, everolimus was combined with an anti-estrogen drug using similar criteria as Phase 1 trials (NCT02291913). In the Phase 2 LEO trial, everolimus is combined with letrozole and leuprorelin following disease progression with tamoxifen with or without a GnRH agonist (NCT02344550). In the Phase 3 MAIN-A study, everolimus is combined with an aromatase inhibitor as part of a maintenance regimen for $HR^+/HER2^-$ BCBM following treatment with one line of chemotherapy (NCT02511639).

3.3.5 Estrogen pathway antagonists—In addition to the trials listed above, anastrozole is being combined with the CDK4/6 inhibitor palbociclib in a Phase 2 study (02942355). In the phase 3 FEVEX study, fulvestrant is followed by exemestane and everolimus in the setting of symptomatic BM (NCT02404051). In a phase 2 study, fulvestrant is being investigated with and without ganetespib (NCT01560416). Fulvestrant is being utilized with/without lapatinib in a Phase 3 study (NCT00390455). Alisertib (MLN8237), an Aurora A kinase inhibitor, proved to be ineffective in Phase III trials, but is now being combined with fulvestrant in a Phase I study (NCT02219789).

GDC-0810, a selective estrogen receptor degrader, is being tested in a Phase 1 and 2 study as monotherapy and in combination with palbociclib and/or a luteinizing hormone-releasing hormone agonist (NCT01823835). Elacestrant (RAD-1901), another selective estrogen

receptor modulator, is in two Phase 1 studies for HR^+ BCBM patients that have progressed on at least 1 line of hormone therapy (NCT02650817, NCT02338349). Z-Endoxifen is being utilized in a Phase 1 study on participants with HR^+ solid tumors and those with metastatic disease must have had at least one prior chemotherapy treatment (NCT01273168).

3.3.6 VEGF inhibitors—Cabozantinib, an inhibitor of c-Met and VEGFR2, is being trialed with and without trastuzumab in BCBM patients in a Phase II study that spans across HR+, HER2+, and triple-negative subtypes (NCT02260531). In another Phase II study, cabozantinib is combined with fulvestrant (NCT01441947). Lenvatinib, a tyrosine kinase inhibitor against VEGFR receptors, is being combined with letrozole in a phase 1 and 2 study on asymptomatic HR^+ BCBM (NCT02562118).

3.3.7 Insulin-like growth factor receptor antibodies—Xentuzumab (BI836845), an insulin-like growth factor receptor 1 antibody, and abemaciclib are being investigated with and without hormonal therapy (NCT03099174). The insulin-like growth factor-1 inhibitor BMS-754807 completed a Phase II study where it was tried with and without letrozole, but results have not been published (NCT01225172).

3.4 Triple Negative

The absence of ER, PR, and HER2 receptors (ER^-, PR^-, $HER2^-$) in breast cancer cells is termed triple negative or the basal subtype. Triple negative breast cancer (TNBC) is aggressive and tends to affect younger women. Due to the lack of targeting options, TNBC often has a high rate of recurrence and a worse prognosis than other breast cancer subtypes. [75–77] TNBC make up approximately 30% of all BCBM, with approximately 40% of metastatic TNBC eventually developing brain metastases. [78] As such, therapy is primarily with systemic cytotoxic therapy. TNBC typically have an initial response to chemotherapy that often relapses to cause large numbers of chemoresistant metastases. [79]

3.4.1 Systemic Chemotherapy—Chemotherapy clinical trials have typically excluded patients with brain metastases for a variety of reasons, including limited penetration of agents through the BBB and BTB, the lack of a convenient modality for tumor burden monitoring, and poor overall survival prognoses leading to negative outcomes for patients [80]. Some of the earliest published work in chemotherapy for brain tumors began in the 1950s and 1960s, focusing on use of systemic agents such as methotrexate, thioTEPA, nitrosoureas, and vinca alkaloids. [81–84] Kofman *et al* noted the use of prednisolone to reduce neurological symptoms in 1957. [85] Though the chemotherapy field has advanced, a regimen specific for the treatment of BCBM has yet to be approved and ratified by the Food and Drug Administration (FDA) or national and international cancer organizations. Systemic cytotoxic therapy including taxanes (docetaxel, paclitaxel), anthracyclines (doxorubicin), platinum compounds (cisplatin), and alkylating agents (cyclophosphamide) in combination with other agents have shown some efficacy in small studies. [86–89] The rise of novel dosage forms, immunotherapy, and small molecule inhibitors has pushed the envelope of treatment expectations and produced trials focusing specifically on BCBM.

3.4.2 Traditional Chemotherapy—Various combinations of cisplatin, etoposide, doxorubicin, 5-fluorouracil, methotrexate, vincristine, teniposide, lomustine, irinotecan, gemcitabine, paclitaxel, and temozolomide have been trialed in BCBM patients. Of these combinations, cisplatin-etoposide [90] alone or pretreated with bevacizumab [91], cisplatin-cyclophosphamide [92], cisplatin-vinorelbine [93], and cisplatin-gemcitabine [94] showed significant efficacy. Full descriptions of nonspecific chemotherapeutic regimens and descriptions are provided in Table 3.

Based on clinical trials, cisplatin has become the backbone for treating both primary BC as well as BM. Cisplatin, bevacizumab, and etoposide were combined for a Phase II trial of 8 BCBM patients in Taiwan, showing effect in 5 [95]. Cisplatin is being combined with veliparib, a PARP-inhibitor, for treating triple-negative and BRCA-mutated BC and associated BM (NCT02595905). As a single agent, temozolomide has been explored to treat brain metastases of breast cancer, lung cancer, and melanoma (NCT00831545) Eribulin, though not a targeted agent, is noted for its potential response in both triple-negative and $HER2^+$ patients, and is being studied in a Phase II trial in the treatment of $HER2^+$ BCBM (NCT02581839). Figure 3 illustrates the mechanism of traditional chemotherapy.

3.5 $HER2^+$

HER2 overexpression is found in 20-25% of all breast cancer cases [96]. As a plasma membrane-bound receptor tyrosine kinase (RTK), HER2 upregulation increases signaling from the extracellular environment for promotion of cellular survival and proliferation through a variety of downstream effectors [97]. Significantly, the $HER2^+$ and TNBC subtypes have been shown to metastasize to the brain at higher rates than other BC subtypes [98–101]. The enhanced extracranial systemic management of $HER2^+$ metastatic BC with HER2–therapies trastuzumab and pertuzumab in addition to chemotherapy has contributed to the increased incidence of BM in this group [97]. One of the major pathways involved in the HER2–targeted therapy resistance essential to survival of $HER2^+$ BC cells that colonize the brain is that of PI3K. The PI3K pathway that transmits signals of cell cycle progression and survival to the central circuitry of the cell is over-activated via the mechanisms of PTEN loss and acquisition of activating mutations in the PI3K gene in trastuzumab-resistant BC [102–104].

3.5.1 HER2+ Therapy—Treatment of $HER2^+$ metastatic breast cancer with pHER2-targeted monoclonal antibody rhuMAb was first shown to have efficacy in patients who had received extensive prior chemotherapy in a Phase II study conducted by Baselga et al. in 1996 [105]. Two years later a phase 2 study showed that the combination of rhuMAb and cisplatin produced higher clinical response rates in metastatic BC patients than either as a monotherapy [106]. Just a few years later in 2001, Slamon et al. demonstrated that HER2–targeted monoclonal antibody trastuzumab in addition to either an anthracycline and cyclophosphamide combination, paclitaxel, or chemotherapy compared to each alone produced significantly longer progression-free survival (PFS) [107]. Recently in 2015, Swain et al. reported the most recent analysis of the CLEOPATRA trial [77] in which pertuzumab, a monoclonal antibody targeting a different epitope on the extracellular portion of HER2 than trastuzumab, was added to trastuzumab and docetaxel for the treatment of

metastatic BC [108]. The addition of pertuzumab improved overall survival (OS) by 15.7 months to 56.5 months in treatment-naive patients, supporting the use of this triplet therapy in the clinic [108].

The increasing incidence of $HER2^+$ BC metastasizing to the brain necessitates an intense focus on the treatment of these lesions. According to the American Society of Clinical Oncology 2014 Clinical Practice Guidelines for the treatment of $HER2^+$ metastatic BC and BM, patients should receive local therapies including surgery, whole-brain radiotherapy, and stereotactic radiosurgery, and systemic therapy if indicated [109]. Many groups have investigated the roles of systemic chemotherapy, targeted therapy, immunotherapy, or a combination of these for the treatment of $HER2^+$ BCBM. The registHER study found that $HER2^+$ BCBM patients treated with chemotherapy vs. no chemotherapy had greater OS (16.4 vs. 3.7 months) and patients treated with trastuzumab had greater OS (17.5 vs. 3.8 months) [110]. Multiple studies have shown patients with $HER2^+$ metastatic BC with BM who received trastuzumab have improved survival due to better extracranial systemic management of $HER2^+$ metastatic BC. Unfortunately, trastuzumab is less effective in controlling $HER2^+$ CNS metastases [111–113]. Later it was found that the combination of lapatinib and capecitabine extended OS for $HER2^+$ BCBM patients compared to trastuzumab alone [114, 115]. Further, Phase 2 results from the LANDSCAPE study indicated that combining lapatinib and capecitabine for first-line treatment of $HER2^+$ BCBM showed activity by providing objective CNS responses in 65.9% of patients [116]. Most recently, ado-trastuzumab emtansine (T-DM1), a trastuzumab molecule conjugated to a cytotoxic microtubule-destabilizing agent, was associated with longer OS when compared to the combination of lapatinib and capecitabine [117]. T-DM1 significantly improved OS vs. treatment of physician's choice in $HER2^+$ metastatic breast cancer following two or more HER2-targeted treatment regimens in the phase 3 open-label TH3RESA trial [118]. To support the efficacy of T-DM1 in the treatment of $HER2^+$ BCBM, a handful of small trials and case studies have reported promising results [119–123]. Perhaps the most encouraging results to date are those from the ongoing phase 3b KAMILLA study of T-DM1 in $HER2^+$ BCBM patients which show that T-DM1 treatment decreases the size of brain target lesions in 84 of 126 patients with measurable CNS lesions [124]. Table 4 lists results of completed HER2+ BCBM clinical trials.

3.5.2 Novel Chemotherapy for HER2+ Brain Metastases—The future of pharmacological intervention for the treatment of $HER2^+$ BCBM looks bright, however many challenges remain. These include determining the precise BTB permeability of T-DM1 in $HER2^+$ BCBM and to ascertain the mechanistic contributions of the trastuzumab molecule and DM1 molecule in conferring the cytotoxic actions of T-DM1 in the brain TME. The concurrent use of radiosurgery and T-DM1 elicited a 75% response rate in a small group of patients with $HER2^+$ BCBM (n=4): one complete response, one partial response, one stable disease, and one progression [125]. This report is supported by mechanistic data showing that T-DM1 provides potent and tumor selective radiosensitization [126]. The rational combination of T-DM1 with targeted therapies that inhibit over-activated pathways in $HER2^+$ metastatic BC has also been an area of interest. A phase 1 study of T-DM1 in combination with alpelisib (BYL-719), an oral PI3K inhibitor, showed that the combination

was safe and provided significant anti-tumor activity in metastatic BC patients previously treated with trastuzumab and taxane therapy [127]. It will be of great interest to determine whether combining T-DM1 with BBB-permeable targeted therapies that inhibit over-activated pathways in $HER2^+$ BCBM confers greater benefit than T-DM1 alone. A phase 1b trial combining trastuzumab with PI3K inhibitor, buparlisib, showed an impressive disease control rate (75%) in $HER2^+$ metastatic BC and supported the continuation to a phase 1b/2 trial including BM patients (NCT01132664) [128]. While this trial was ultimately terminated, many of the preclinical and clinical studies referenced above support a trial combining T-DM1 with a PI3K inhibitor (alpelisib or BBB-permeable buparlisib) for the treatment of $HER2^+$ BCBM patients.

There are varieties of planned, recruiting, and active clinical trials for the treatment of $HER2^+$ BCBM patients. The combination of everolimus, trastuzumab, and vinorelbine in treating this cohort is currently being investigated (NCT01305941). Others are seeking to determine whether T-DM1 in combination with metronomic temozolomide compared to T-DM1 alone confers secondary prevention of $HER2^+$ BCBM following stereotactic radiosurgery (NCT03190967). An ongoing phase II study is looking at the efficacy of lapatinib for the treatment of $HER2^+$ BCBM that have progressed following radiation treatment using whole brain radiotherapy (WBRT) or stereotactic radiosurgery (SRS) to the brain (NCT00263588). A planned phase II study by the Jules Bordet Institute will determine whether T-DM1 (Kadcyla) is effective in treating $HER2^+$ BCBM (NCT03203616). To test whether HER2-targeted therapy resistance is a factor in the relative ineffectiveness of trastuzumab and pertuzumab for the treatment of $HER2^+$ BCBM, a phase I trial will assess the combination in patients with new untreated asymptomatic or low symptomatic $HER2^+$ BCBM (NCT02598427). A phase I study of T-DM1 in combination with sequential whole brain radiotherapy was competed, however no results have been posted yet (NCT02135159). Another phase I study is observing the effect of ARRY-380 (HER2-targeted agent that appears to have some brain penetration) in combination with trastuzumab for the treatment of $HER2^+$ BCBM (NCT01921335). A phase I study combining lapatinib, WBRT, and trastuzumab reported a median PFS of 4.8 months and median OS of 18 months in $HER2^+$ BCBM patients (NCT00470847). The combination of neratinib (HKI-272) and capecitabine is currently being used in a phase II study at Dana-Farber Cancer Institute for the treatment of $HER2^+$ BCBM (NCT01494662). The phase I LAPTEM trial combined lapatinib and temozolomide for the treatment of progressive $HER2^+$ BCBM, however no results have been posted (NCT00614978). A phase II study of local therapy (SRS and/or neurosurgery) is planned for the treatment of up to 5 BMs in individual $HER2^+$ BC patients (NCT02898727). The phase II Lux-Breast 3 study demonstrated that afatinib alone or in combination with vinorelbine did not produce better outcomes than treatment of physician's choice (TPC) (NCT01441596). A phase II trial sponsored by Northwestern University is recruiting patients with $HER2^+$ BCBM to be treated with a combination of palbociclib and trastuzumab (NCT02774681). Another phase II study by the National Cancer Institute (NCI) is recruiting patients to explore the combination of WBRS/SRC in combination with lapatinib for the treatment of $HER2^+$ BCBM (NCT01622868). Yet another phase II study is recruiting patients with $HER2^+$ BCBM to test the effectiveness of cabozantinib +/− trastuzumab (NCT02260531). Lastly, the combination of tucatinib, capecitabine, and

trastuzumab will be compared to placebo, capecitabine, and trastuzumab in the phase 2 HER2CLIMB trial (NCT02614794). Table 5 outlines in-progress and upcoming HER2+ trials that include BM patients. Figure 3 illustrates mechanism of HER2+ therapeutics.

4. Formulations involved in treating brain metastases

The BBB provides considerable resistance to chemotherapeutic agents. Specific physicochemical properties allow drugs access into the brain. General characteristics that promote BBB permeation have been summarized to have an optimal molecular weight 400-600 Da, higher lipophilicity and lower participation in hydrogen bonding. In an attempt to increase BBB permeability, chemical modification of drug molecules by charge reduction and addition of lipophilic moieties is a common approach. The BBB itself can be chemically targeted so that it transiently allows the passage of therapy across. Compounds such as bradykinin [129] and its synthetic analogs [130], interleukin-2 [131], and leukotriene C4 [132] have been used to open tight junctions as well as osmotic agents such as mannitol. However, this approach comes with the risk of adverse and of infections due to a compromised BBB. Adenosine receptor agonists using a dendrimer-based delivery have also been used to briefly open the BBB, reducing complications [133].

Nanotechnology has become one of the defining standards in the development of “novel” therapeutic agents. Use of nanometer sized carriers for targeted delivery of chemotherapeutic drugs to brain metastases is one of the most commonly investigated approaches. Polymeric nanoparticles, solid-lipid nanoparticles, micelles, and liposomes are some of the delivery systems that can be used to achieve drug entry through the BBB. These novel drug delivery systems can be used to achieve spatial (site-specific) as well as temporal (time-dependent) control over treatment of brain metastases of breast cancer. Active targeting of the drugs can be achieved by delivering them via multifunctional nanoparticles. These systems have tumor specific moieties on their surface, which directs the carrier to the tumor site, where the drug is released. The main hypothesized advantage of using nanocarriers for cancer therapy is the Enhanced Permeation and Retention (EPR) effect. This concept was first laid down by Matsumura and Maeda, when they studied the tumor accumulation of a polymer conjugated protein neocarzinostatin, and a series of radiolabeled proteins of varying sizes [134]. Macromolecules tested were found to have a greater accumulation and longer retention in tumor tissue, as a function of their size. The observed phenomenon was attributed to twin effects [135].

Tumor vasculature is leaky due to rapid angiogenesis and elevated levels of vascular permeability factors, facilitating the permeation of macromolecules into the tumor tissue. Additionally, the absence of proper lymphatic drainage supports longer retention of chemotherapy at the tumor site. This effect can be applicable to drug delivery systems such as nanoparticles, micelles, and liposomes [136]. The EPR effect is attributed to liposomal and nanoparticulate formulations showing tumor site accumulation. Unfortunately, adequate evidence does not exist for the EPR phenomenon. Only one clinical study showed accumulation of radiolabeled PEGylated liposomes in tumor tissues, an indication of the EPR effect [137].

A mathematical model to quantify the EPR effect was developed based on pharmacokinetic data from the clinical trials of the FDA approved PEGylated liposomal formulation of doxorubicin, Doxil® [138]. This pharmacokinetic model considered the tumor as a separate compartment, and introduced rate constants for extravasation, as well as intravasation. The tumor accumulation of Doxil was significantly higher compared to that of conventional doxorubicin. It has been determined that drug delivery systems should preferably be biocompatible materials, a size of at least 40 kDa or more for the EPR effect to be applicable [139], with the caveat that heterogeneity within the tumor tissue, and among tumor types, makes the EPR effect variable. Some of the parameters responsible for variable EPR effects include low systolic blood pressure, hypoxia, presence of emboli, and vascular density [140]. This phenomenon can be erratic with micellar and liposomal drug delivery systems, as they need to maintain system stability until they reach the site of action. The EPR effect has been used to predict therapeutic outcomes, but is not a reliable marker [140].

The therapeutic effect of the drug is a downstream effect that is dependent of other factors such as drug release and drug uptake. To make EPR more uniform, its augmentation has been described in rodents as well as humans using elevation of blood pressure [141]. Due to its heterogeneity, the EPR effect has been unsuccessful in a clinical setting, a stark contrast to its efficiency in pre-clinical murine models [142]. Better characterization of the EPR effect is required to create uniformity and reliability in clinical scenarios. Regardless of EPR in humans, nanoparticle based drug delivery systems still have relevance in terms of reducing the toxicity of chemotherapy drugs, localized delivery and imaging of tumor microenvironment [142].

5. Drug delivery systems intended to target brain metastases

5.1 Liposomes

Liposomes are a drug delivery vehicle that consists of a phospholipid bilayer containing an inner, aqueous pocket. Hydrophilic drugs or imaging agents may be incorporated into the aqueous compartment, or hydrophobic ones in the lipid bilayer [143]. There are multiple types of liposome structures that may form when phospholipids are suspended in aqueous solution, including micelles and multilamellar or unilamellar vesicles. These liposomes may be generated via multiple methods; the most common being thin lipid film hydration. Freeze-thaw cycles, sonication, and extrusion through filters are additional procedures which may be used to control the vesicle type and size distribution [144]. Typically, liposomes used for clinical drug delivery are constructed from endogenous lipids such as cholesterol or their synthetic derivatives, have a size on the order of 100 nm diameter, and are unilamellar in structure [145, 146].

The use of liposomes provides an opportunity for targeted drug delivery. Targeting ligands such as homing peptides and whole antibodies or their fragments, may be inserted on the surface of the liposomes [147]. This targeting confers liposomes the ability to potentially cross the BBB by adsorptive-mediated transcytosis (AMT) and receptor-mediated transcytosis [148]. AMT is a nonspecific mechanism in which the cationized surface of liposomes may interact with the anionic glycocalyx, stimulating their endocytosis and transport to the abluminal portion of the endothelial cell where they are exocytosed into the

interstitial fluid of the CNS [149]. Receptor-mediated transcytosis works through a similar mechanism whereby receptors on the luminal surface of the endothelium, such as the insulin, transferrin, and LDL receptors, may bind to liposomes which have been labeled with ligands or antibodies for these receptors [147–152]. These processes may result in three different fates for the liposome: they may pass through the endothelial cell completely and enter the brain, they may stay inside the endothelial cell, or they may be returned to the lumen of the vessel. These transcytotic pathways of BBB penetrance are the predominant pathways for liposomes because paracellular diffusion is limited by tight junctions and particle size [152–158].

One common problem with nanoparticle vehicles, including liposomes, is their rapid clearance by the reticuloendothelial system. This problem is ameliorated in the case of liposomes by incorporating PEG into the lipid membrane [159]. While PEGylation provides more opportunities for attachment for targeting moieties and may reduce clearance, immunogenicity, and antigenicity, it can have negative effects, such as the increased accumulation in the skin, increasing the risk of developing hand-foot syndrome with some formulations. Non-PEGylated liposome formulations have also been developed, which overcome reticuloendothelial system clearance and immunogenicity [151].

Preclinical data using a mouse model of brain metastases demonstrated a PEGylated liposomal formulation of irinotecan (MM-398) greatly enhanced its cytotoxic effect compared to conventional irinotecan [160]. Liposomal formulations of anthracyclines, such as Doxil®, show improved efficacy and toxicity profiles in comparison to conventional formulations [161]. Several drug formulations including liposomes have already received FDA approval. These include liposomal preparations of cancer drugs such as doxorubicin (Doxil®), daunorubicin (DaunoXome®), irinotecan (Onivyde®), and vincristine (Marqibo®), which are being explored in the treatment of BCBM. Liposomal formulations developed for brain metastases have yet to be approved, but clinical trials using glutathione PEGylated liposomal doxorubicin (NCT01386580] and liposomal cytarabine (NCT00992602) are underway.

Doxil® is a marketed formulation of doxorubicin, delivered using PEGylated liposomes. The addition of PEG imparts a ‘stealth’ feature to the nanosystem, by allowing it to avoid premature clearance via the RES. A modified version of Doxil®, was developed with an additional coating of glutathione [152]. Active transport of glutathione across the BBB helped enhance doxorubicin accumulation at the metastatic sites, as well as prolong circulation time. Doxorubicin bound to polysorbate 80-coated butyl cyanoacrylate nanoparticles was found to cross the intact BBB and reach therapeutic levels in the rat brain [162]. A multifunctional theranostic nanosystem was developed for the delivery of doxorubicin and diagnostic agents for brain metastases [163]. The system consisted of a terpolymer comprised of poly(methacrylic acid) and polysorbate 80 on a starch scaffold.

5.2 Conjugating nanoparticles

Housing therapeutics inside 10 nm to 100 nm carriers allow for smaller doses to be given that simultaneously achieve similar or enhanced efficacy, a reduction in side-effect profile, prolonged dosing intervals, and enhanced accumulation compared to their conventional

chemotherapy counterpart [164]. The carriers are often pegylated liposomes as described above, but conjugation to proteins such as transferrin or albumin are also used clinically. Paclitaxel has been formulated as polyethoxylated albumin bound nanoparticles (Abraxane®) and its published phase II [165] and phase III [166] clinical trials reported significant anti-tumor activity compared to standard paclitaxel. It targets the tumor by transcytosis, mediated by the albumin receptor (gp-60). The formulation, devoid of Cremophor EL solvent, was found to be safer. Microemulsion derived nanoparticles of paclitaxel have been prepared using cetyl alcohol and polysorbate as materials [167]. When tested in a rat model, the drug was shown to have an increased brain uptake and toxicity against P-gp expressing cancer cells, indicating a possible protection of paclitaxel from P-gp mediated efflux. Nanoparticles can also be used to house genetic therapy. A Phase I trial of nanoparticles housing the Rexin-G anti-cyclin G1 construct in the treatment of recurrent or metastatic breast cancer was started in July 2007, but no study results are posted as of 2011 (NCT00505271).

Conjugation of chemotherapy to other small molecules allows for targeting. Preclinical models of BCBM were found to have a prolonged survival when treated with nanoconjugates of paclitaxel and hyaluronic acid [168]. This formulation exploited passive diffusion across the BBB, and active tumor cell uptake due to the affinity of hyaluronic acid for CD44 receptors. The active targeting was aimed at circumventing the P-gp efflux that is observed with paclitaxel. Active targeting of mitoxantrone was achieved by targeting the LDL receptor related protein using angiopeptide-2 ligand conjugated on the surface of fluid membrane liposomes [153]. This formulation was found to have improved therapeutic potential in experimental brain metastasis model of breast cancer.

5.3 Pegylation

Polyethylene glycol (PEG) moiety attachment has been a frequent method employed by the pharmaceutical industry for nearly four decades to improve the systemic circulation of bioactive molecules with poor pharmacokinetic profiles [169]. PEGylation refers to the covalent adherence of multiple linear or branched polyethylene glycol molecules to a drug product [170]. PEGylation has been utilized in small molecules, liposomes, carbohydrates, enzymes, nucleotides and other nanotherapeutic strategies [171–173]. The most common molecule used during the PEGylating process is methoxy-polyethylene glycol (mPEG) [170]. Much like liposomes, the EPR effect can be exploited in the cancer setting. Large macromolecular therapies are able to passively enter tumors due to the presence of neo-angiogenesis and degree of permeability within tumor vasculature [135].

PEG is known to enhance the pharmacokinetics of poorly circulating chemotherapeutics. In the case of the brain, PEG has been shown to increase the concentration of cytotoxic drugs reaching brain tissue [152]. PEG is also shown to enhance the bioavailability of orally available drugs by protecting them from catalytic degradation [174].

While PEGylation also reduces the toxicity profile of many chemotherapeutic agents [175, 176], this is not without its own drawbacks. After undergoing IV administration of PEGylated nanomedicines and small molecules, clotting and clumping can occur, initiating a cascade of detrimental side effects, such as embolism [177]. Hypersensitivity to PEGylated

therapies is also an important concern. The complement activation cascade of the immune system is thought to play a role in immunogenicity of PEG molecule, which may lead to anaphylactic shock [178, 179]. Hypersensitivity can also be observed in the gastrointestinal tract and to dermatological preparations containing PEG [180–184].

Another side effect to PEGylating compounds is the accelerated blood clearance (ABC) phenomenon. In the first mention of the ABC phenomenon, PEGylated liposomes were cleared at an accelerated rate during subsequent injection [185]. This observed effect further potentiates the idea of the immune system playing an important role in reaction to PEG molecules. The accelerated clearance may also indicate that size plays an important role, as previous experiments have shown that size is an important factor when considering ABC [186]. Perhaps, larger PEG molecules may elicit this effect to a greater degree. ABC is a poorly understood mechanism and warrants further research in regard to PEG.

PEG is an attractive therapeutic approach in cancer. Limiting systemic toxicity could provide many benefits to cytotoxic therapeutics. Oncaspar® (pegaspargase), an L-asparaginase that is covalently conjugated to PEG and mPEG, is FDA-approved for the treatment of acute lymphoblastic leukemia [187], though no clinical trials are planned for BCBM. Another PEGylated therapy being clinically investigated for BCBM is etirinotecan pegol (NKTR-102). This novel therapy is a four-armed PEG polymer, with each arm ending with a hydrolysable ester linker and an irinotecan molecule [188]. In its preclinical studies, NKTR-102 was found to increase the duration of exposure and accumulation of SN-38 (the active metabolite of irinotecan) into tumors when compared to conventional irinotecan. [188]. NKTR-102-treatment improved survival in a triple-negative brain metastatic model compared to conventional chemotherapy agents [189]. In the ATTAIN trial, BCBM patients are being recruited to test the efficacy of NKTR-102, with a primary outcome of CNS disease control rate (NCT02915744).

Another PEGylated cancer therapeutic which has completed an open-label, PhaseI/IIa clinical trial is glutathione PEGylated liposomal doxorubicin (2B3-101). 2B3-101 showed favorable improvements in overall survival in its preclinical studies over both PEGylated liposomal doxorubicin and vehicle [152]. 2B3-101 is thought to have increased targeting capabilities due to the presence of the glutathione acting as a targeting ligand [152]. The recently completed trial, for which no results have been reported as of yet, assessed the safety and tolerability of 2B3-101 in patients with brain metastases of solid tumors and malignant glioma over 16 months as well as its combination with trastuzumab in patients with HER2+ BCBM.

5.4 Physical devices

Several other therapeutic approaches hypothesized for treatment of primary brain tumors can be extrapolated to treat metastatic tumors as well. These include use of convection-enhanced therapy, Giladel® (carmustine) wafers, osmotic BBB disruption, and ultrasound mediated BBB opening [190]. Ultrasound mediated disruption of BBB has been found to be effective in enhancing large molecule delivery, such as trastuzumab therapy [191]. This technique has been combined with using nanocarriers for drug delivery in brain metastases of breast cancer. Ultrasound induced hyperthermia has been employed to deliver doxorubicin

encapsulated in a liposomal carrier for brain metastasis of breast cancer [192]. Significantly higher doxorubicin was measured in tumors with the combination as compared to treatment with doxorubicin liposomes alone.

6. CONCLUSION

The discovery of new biological targets has led to a resurgence and expansive interest in chemotherapy and dosage forms. New agents inhibiting PARP, CDK 4/6, PI3K, ILGF-1, estrogen pathways, HDAC, and $HER2^+$ receptors and downstream effects, are being combined with traditional options such as radiation and surgery to develop new strategies to treat BCBM. Liposomes, conjugation to polymers, and nanoparticle sizing offer a route to repurpose conventional chemotherapy via the enhanced permeation and retention effect, which leads to reduced side effects, longer therapeutic windows, and less-frequent dosing intervals. With the combination of improved pharmacokinetic profiles and targeted chemotherapy, clinical trials are including patients with BCBM more frequently, and may provide substantial therapeutic advances to significantly extend overall survival for this diagnosis.

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Abbreviations

ABC	accelerated blood clearance
BBB	blood-brain barrier
BCBM	breast cancer brain metastases
BTB	blood-tumor barrier
CNS	central nervous system
CDK	cyclin-dependent kinase
EPR	enhanced permeation and retention
ER	estrogen receptor
HDAC	histone deacetylase
HER2	human epidermal growth factor receptor 2
Hormone receptor	HR
mTOR	mammalian target of rapamycin
OS	overall survival

P-gp	permeability glycoprotein
PARP	poly-ADP ribose polymerase
PEG	polyethylene glycol
PFS	progression-free survival
PI3K	phosphatidylinositide 3-kinase
PEG	polyethylene glycol
PR	progesterone receptor
SRS	stereotactic radiosurgery
T-DM1	trastuzumab emtansine
TNBC	triple negative breast cancer
VEGF	vascular endothelial growth factor
WBRT	whole-brain radiation therapy

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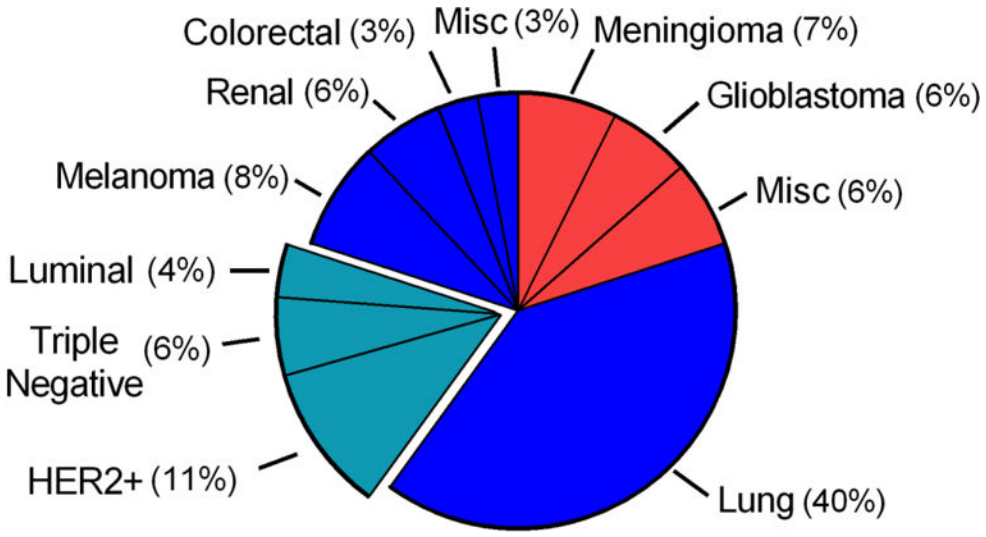

Fig.1.

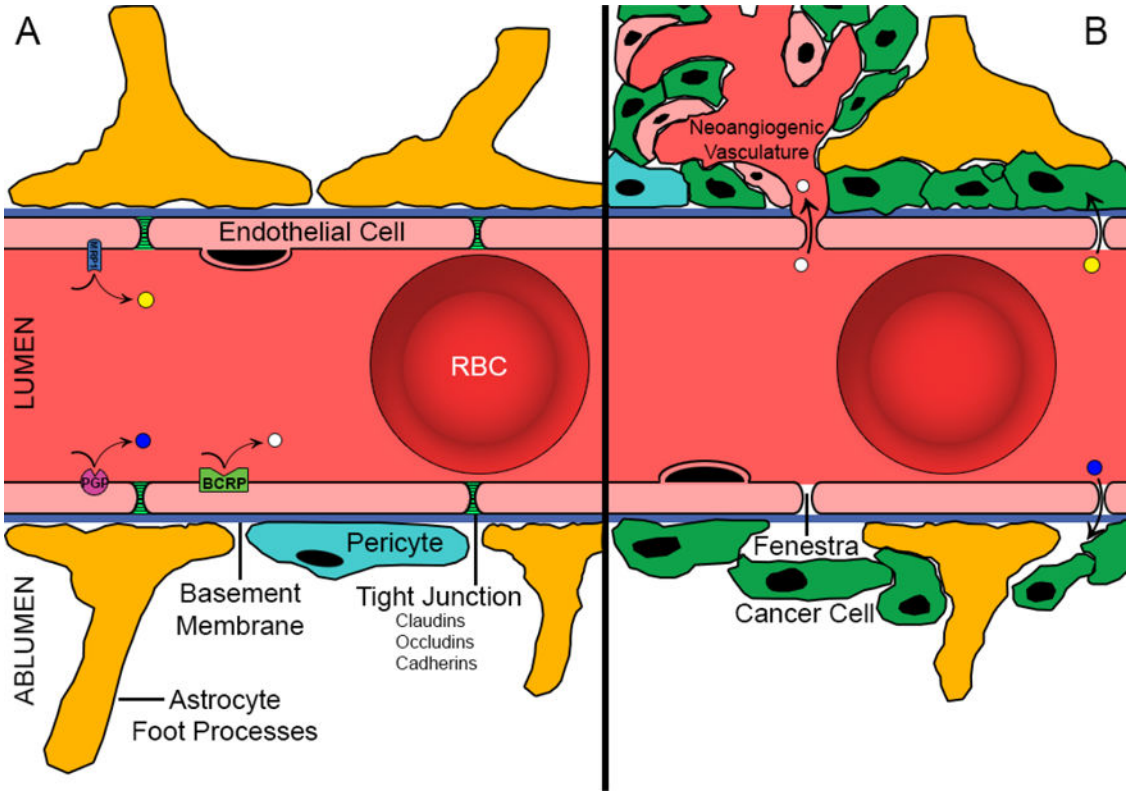

Fig.2.

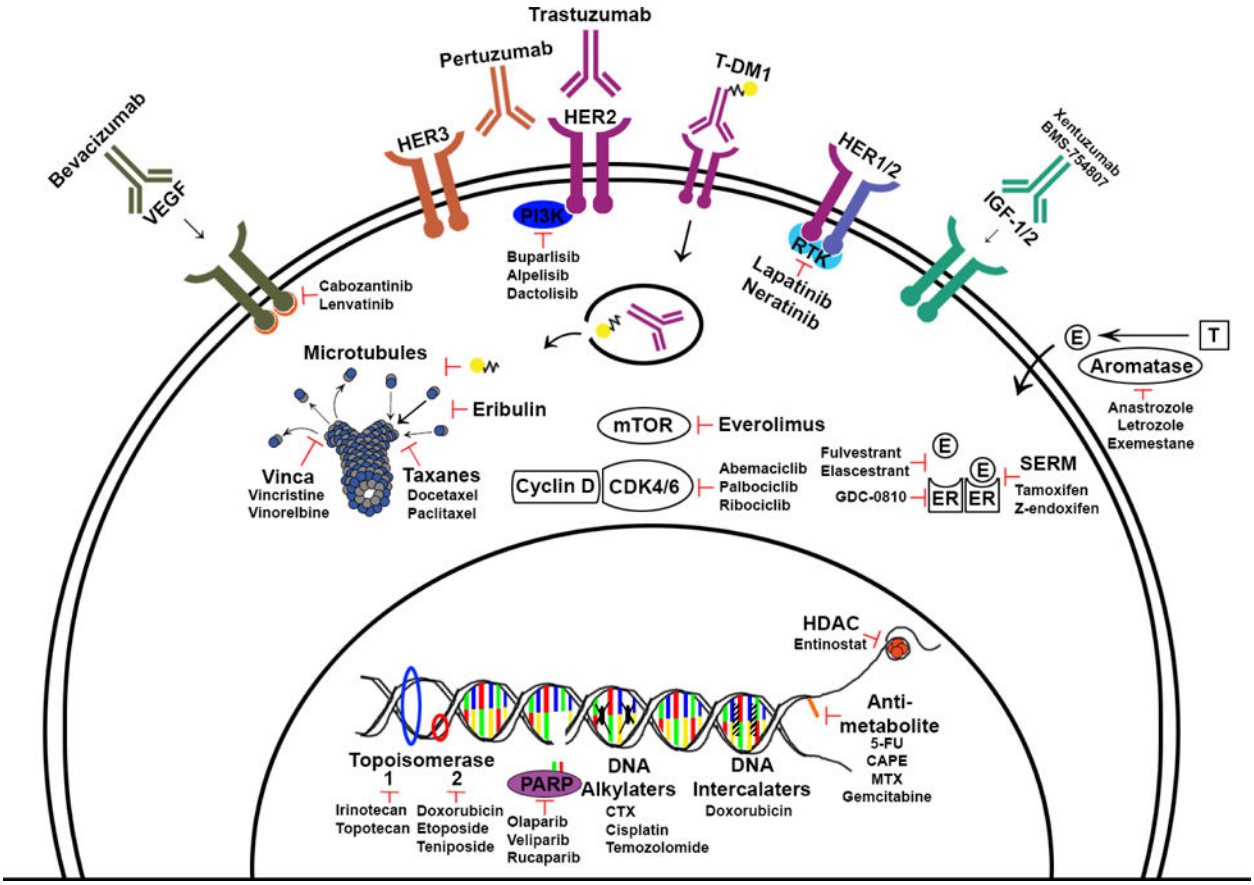

Fig.3.

Table 1
Results of hormone positive BCBM clinical trials

Compared to standard chemotherapy, targeted agents have a better response rate and newer agents have fewer side effects.

Compound	Combination	Outcomes	Summary
Anastrozole	Gefitinib	In a Phase II study, 108 patients received anastrozole with gefitinib or placebo. The PFS at 1 year was 35% with gefitinib and 32% with placebo while the median duration of response was 13.8 months with gefitinib and 18.6 months with placebo. The most common AE was fatigue (35%), rash (32%), diarrhea (31%), dry skin (27%), and myalgia (27%) [193].	
5-Azacitidine	Entinostat	In a Phase II study, 27 patients with HR+ and 13 with TN MBCB received the combination. There was one PR in the HR+ group (ORR =4%), none in the TN group, and one PR in an optional continuation group (n=12) [194].	This combination was well-tolerated but the primary endpoint (ORR ≥20%) was not achieved.
Buparlisib	Fulvestrant	In a Phase I trial, 31 patients received this combination to determine the MTD of buparlisib and assess preliminary efficacy. Of the 29 evaluable patients, the clinical benefit rate was 58.6%. Commone AE were fatigue (38.7%), elevated hepatic enzymes (35.5%), rash (29%), & diarrhea (19.4%) [195].	
	Fulvestrant	In a Phase III trial, 576 patients received this combination with median PFS of 6.9 months vs. 5 months in placebo group. The most common grade 3–4 AE were increased hepatic enzymes (~25%), hyperglycemia (15%), and rash (8%) [196].	The results show that PI3K inhibition combined with endocrine therapy is effective but no further studies are being pursued with this combination due to the toxicity. Patients' disease had to progress on or after an AI and up to one prior line of chemotherapy.
	Paclitaxel	In a Phase III & III trial, 207 patients received this combination and 209 received a placebo with paclitaxel to measure PFS in Phase 2 before progressing to Phase 3. The PFS with buparlisib was 8 months vs. 9.2 months with placebo. The trial did not enter Phase 3 due to futility [74].	
Cabozantinib		In a Phase III discontinuation study, 45 patients received cabozantinib as a 12-week lead-in stage followed by a randomization stage to continue cabozantinib or receive placebo. During the lead-in stage, ORR was 13.6% and disease control rate at week 12 was 46.7%. The overall median PFS was 4.3 months and median OS was 11.4 months [197].	Active brain metastasis was excluded but cabozantinib demonstrated clinical activity in objective response and disease control.
Capecitabine		In a Phase III trial, 546 patients with MBCB received capecitabine. Overall survival was 14.5 months and PFS was 4.2 months and 25 patients developed new BCBM [66].	Capecitabine appears to cross the BBB and have activity in BCBM.
	Sunitinib	In a Phase II trial, 12 patients with BCBM first received capecitabine with radiation therapy followed by capecitabine with sunitinib. The trial was closed due to slow accrual but median PFS was 4.7 months and OS was 10 months [67].	There was no extension of PFS and this combination was considered significantly toxic.
		In a prospective study, 8 BCBM patients received capecitabine 2–3 hours before surgical resection of BCBM tumor to assess drug levels in BCBM tissue. There were measurable amounts of capecitabine and its metabolites in BCBM tissue but BCBM to serum ratio was higher for 5-fluorouracil than capecitabine [68].	Capecitabine was able to penetrate the BBB, though to a variable degree.
	WBRT	In this retrospective study, 5 BCBM patients received capecitabine with WBRT. One patient had a complete response, two had partial responses and one had stable disease [64].	
Z-Endoxifen		In a Phase I trial, 38 HR+ endocrine-refractory MBCB patients received Z-Endoxifen. Overall clinical benefit rate was 26.3% [198].	

Compound	Combination	Outcomes	Summary
Eribulin		In a Phase III trial, 544 patients with MBCB received eribulin. Overall survival was 15.9 months and PFS was 4.1 months and 13 patients developed new BCBM [66].	Eribulin does not cross a healthy BBB but may be able to do so in combination with radiation therapy.
		Sixty-six patients with pre-treated MBCB received eribulin monotherapy. Median PFS was 5 months and OS was 8 months, 15 patients had PR, and 36 had stable disease [199].	Eribulin monotherapy was deemed safe and effective as a result of this study.
Estradiol	Exemestane	In a pilot study, 13 patients received estradiol and 6 (46%) had no progression at 3 months and were then switched to exemestane. Of the 6 on exemestane, 5 had disease progression and 1 had stable disease. Median PFS was 4.8 months [200].	
Lapatinib		In a prospective study, 4 BCBM patients received 2–5 doses of lapatinib daily with the last being 2–3 hours before surgical resection of BCBM tumor to assess drug levels in BCBM tissue. The median BCBCM concentrations ranged from 1.0–6.5 μM [68].	Lapatinib was able to penetrate the BBB, though to a variable degree.
Paclitaxel	Pictilisib	In the Phase II PEGGY study, paclitaxel was combined with pictilisib or a placebo for 183 eligible patients. The PFS for the pictilisib group was 8.2 months versus the placebo group which was 7.8 months [201].	
Pilaralisib	Letrozole	In a Phase I & II dose escalation study, 21 patients were enrolled in Phase 1 to determine the MTD and 51 patients were enrolled in Phase II which determined efficacy using the MTD. One patient had a PR and the rate of PFS at 6 months was 17%. The most common grade ≥3 AE were increased hepatic enzymes (5%) and rash (5%) [202].	The safety was acceptable but the efficacy was limited.
Ramucirumab	Eribulin	In a Phase II trial, 141 MBCB patients received a combination of ramucirumab and eribulin or eribulin alone. Median PFS for the combination was 4.4 months versus 4.1 months for eribulin alone while OS was 13.5 months versus 11.5 months and ORR was 21% versus 28% [203].	
Temozolomide	Capecitabine	In a Phase I trial, 24 patients received temozolomide combined with capecitabine. Of the 24 patients, 1 had a complete response and 3 had partial responses (ORR 18%) [63].	
	Vinorelbine	Thirty-six BCBM patients received temozolomide in combination with vinorelbine and WBRT. There were 3 complete responses and 16 PR with an ORR of 52%. The median PFS and OS were 8 and 11 months, respectively [65].	
Voxtalisib	Letrozole	In a Phase I & II dose escalation study, 21 patients were enrolled in Phase I to determine the MTD and 51 patients were enrolled in Phase II which determined efficacy using the MTD. No patients responded and the rate of PFS at 6 months was 8%. The most common grade ≥3 AE were increased hepatic enzymes (11%) and rash (9%) [202].	The safety was acceptable but the efficacy was limited.

AE: adverse events; MBCB: metastatic breast cancer of the brain, MTD: maximum therapeutic dose; ORR: overall response rate; OS: overall survival; PFS: progression-free survival.

Table 2

In-progress and upcoming clinical trials involving hormone-positive BCBM.

Compound	Trial	Phase and Status	Parameters	Comment
Abemaciclib	NCT02308020	Phase II, currently recruiting	Must have brain metastasis from non-small cell lung cancer, melanoma, or HR+ breast cancer that can be HER2+/−.	Leptomeningeal metastases were excluded.
Abemaciclib + Trastuzumb +/− Fulvestrant	NCT02675231 (monarcHER)	Phase II, currently recruiting	Participants with MBCB that is HR+/HER2+ who previously received at least 2 HER2-targeted therapies. CNS metastases were excluded if untreated, symptomatic, or required steroids to manage symptoms.	
Abemaciclib	NCT02792725	Phase unknown, offering expanded access	Participants with HR+/HER2− MBCB. CNS metastases requiring immediate local therapy are excluded.	Participants' MBCB had to progress following anti-estrogen therapy.
Alisertib (MLN8237) + Fulvestrant	NCT02219789	Phase I, ongoing but not recruiting	Participants with HR+ MBCB. CNS metastases treated by surgery and/or radiotherapy and neurologically stable and off steroids >12 weeks are eligible.	
Alpelisib (BYL719) + Fulvestrant	NCT02437318 (SOLAR-1)	Phase 3, currently recruiting	Participants with HR+/HER2− MBCB. CNS metastases were excluded unless they completed treatment >4 weeks prior to study with stable CNS tumor at time of study screening and not taking steroids or enzyme inducing anti-epileptic medications.	Participants' MBCB had to progress on or after an AI.
Alpelisib + Tamoxifen + Goserelin	NCT02058381 (B-YOND)	Phase I, ongoing but not recruiting	Participants with HR+/HER2− MBCB. Symptomatic CNS metastases are excluded.	
Alpelisib + Letrozole	NCT01791478	Phase I, ongoing but not recruiting	Participants with HR+/HER2− MBCB. Symptomatic brain metastases are excluded, must be clinically stable >4	

Compound	Trial	Phase and Status	Parameters	Comment
			weeks post-radiation treatment.	
Anastrozole + Palbociclib	NCT02942355	Phase II, currently recruiting	Participants with HR+/HER2− MBCB. Brain metastases are included if no evidence of progression >4 weeks after CNS-directed treatment.	Combination being trialed as first-line therapy and maintenance therapy.
Apitolisib (GDC-0980) + Paclitaxel +/− Bevacizumab	NCT01254526	Phase I, completed	Participants with MBCB but untreated or active CNS metastases are excluded.	
BMS-754807 +/− Letrozole	NCT01225172	Phase II, completed	Participants with HR+/HER2− MBCB, where those with symptomatic BM were excluded.	Must have disease progression following non-steroidal AI treatment.
Buparlisib (BKM120) + Tamoxifen + Goserelin	NCT02058381 (B-YOND)	Phase I, ongoing but not recruiting	Participants with HR+/HER2− MBCB. Symptomatic CNS metastases are excluded.	
Buparlisib + Fulvestrant	NCT01610284 (BELLE-2)	Phase 3, ongoing but not recruiting	Participants with HR+/HER2− MBCB, where those with symptomatic BM are excluded.	Participants' MBCB had to progress on or after an AI.
Buparlisib + Fulvestrant	NCT01633060 (BELLE-3)	Phase 3, ongoing but not recruiting	Participants with HR+/HER2− MBCB, where those with symptomatic BM were excluded.	Participants' MBCB had to progress on or after mTOR inhibitor.
Buparlisib + Paclitaxel	NCT01572727 (BELLE-4)	Phase II/3, completed	Participants with known HR status and HER2−, where those with symptomatic CNS metastases were excluded.	
Buparlisib + Tamoxifen	NCT02404844 (PIKTAM)	Phase II, ongoing but not recruiting	Participants with HR+/HER2− MBCB, where those with symptomatic CNS metastases were excluded.	Participants had prior treatment with 1–2 antihormonal therapies.
Buparlisib or Dactolisib + Letrozole	NCT01248494	Phase I, completed	Participants with HR+/HER2+/− MBCB, where those with symptomatic BM were excluded. History of BM must be clinically stable >4 weeks post-radiation treatment and >4 weeks after steroid tapering.	Those with HER2+ must have previous treatment with trastuzumab.
Buparlisib + Capecitabine	NCT02000882	Phase II, ongoing but not recruiting	Participants with HR+/HER2−, HER2+, or triple-negative MBCB	At least 1 CNS lesion ≥5mm in at least 1 dimension with prior WBRT.

Compound	Trial	Phase and Status	Parameters	Comment
			with brain metastases.	
Cabozantinib +/− Trastuzumab	NCT02260531	Phase II, currently recruiting	Participants must have CNS lesions but leptomeningeal cannot be the only CNS metastasis.	This study has three arms, HER2+, HR+, and triple-negative.
Cabozantinib + Fulvestrant	NCT01441947	Phase II, ongoing but not recruiting	Participants with HR+/HER2− MBCB with bone involvement. Untreated, symptomatic brain metastases requiring current treatment with steroids and anti-convulsants are excluded.	Participants must have received ≥1 prior line of hormonal therapy or chemotherapy.
Capecitabine + Pegylated Interferon Alfa-2a	NCT00227656	Phase II, terminated (study slow to accrue)	Participants must have CNS metastases that has not progressed on prior treatment with capecitabine, fluorouracil, interferon alfa, or interferon beta.	HR status not specified. Participants must have stable systemic cancer.
Capecitabine + WBRT	NCT00977379 (XERAD)	PhaseII, terminated (insufficient number of participants enrolled)	Participants with known HR/HER2 status and newly diagnosed CNS metastases with at least one lesion ≥1 cm or two lesions 0.5–1 cm.	Leptomeningeal disease is excluded, as is prior treatment for brain metastases.
Capecitabine + Sunitinib + WBRT	NCT00570908	Phase II, terminated (poor accrual)	Participants must have measurable CNS metastases without prior WBRT.	HR/HER2 status not specified.
Capecitabine + AI (Anastrozole or Letrozole or Exemestane)	NCT02767661 (MECCA)	Phase 3, not yet open for recruitment	Participants must have HR+/HER2− MBCB. Known uncontrolled or symptomatic CNS metastases are excluded.	
Dactolisib (BEZ235)	NCT01288092	Phase II, withdrawn prior to enrollment	Participants must have HR+/HER2− MBCB, without symptomatic CNS metastases.	
Elacestrant (RAD-1901)	NCT02650817	Phase I, ongoing but not recruiting	Participants have HR+/HER2− MBCB but symptomatic CNS metastases are excluded.	Tumor progression after ≥6 months of at least 1 line of hormonal therapy.
Elacestrant	NCT02338349	Phase I, ongoing but not recruiting	Participants have HR+/HER2− MBCB but untreated or symptomatic CNS metastases are excluded.	

Compound	Trial	Phase and Status	Parameters	Comment
Z-Endoxifen HCl	NCT01273168	Phase I, currently recruiting	Participants must have HR+ solid tumor of any type and those with brain metastases are excluded unless remained stable ≥3 months after treatment, without steroids or anti-seizure medications.	Participants with MBCB must have had at least 1 prior chemotherapy regimen.
Entinostat (SNDX-275) + Exemestane	NCT02833155	Phase I, currently recruiting	HR+ MBCB in Chinese women and CNS metastases are included if no steroids and stable disease ≥1 month.	Disease progression post-treatment with a non-steroidal AI.
Entinostat + AI	NCT00828854	Phase II, completed	Participants with HR+ MBCB where known active brain metastasis is excluded.	Progressive disease following >3 months treatment with 3rd generation AI.
Entinostat + Erlotinib + Exemestane	NCT01594398	Phase I, completed	Participants with HR+ MBCB or NSCLC and brain metastasis is included if certain criteria are met.	
Entinostat + Nivolumab + Ipilimumab	NCT02453620	Phase I, currently recruiting	Participants must have HER2− MBCB that can be HR+ and brain metastasis is included if stable for >4 weeks and off steroids >2 weeks.	At least 1 prior chemotherapy regimen and 2 lines of hormone therapy.
Eribulin Mesylate +/− Pembrolizumab	NCT03051659	Phase II, currently recruiting	Participants with HR+ MBCB and brain metastases are eligible if they completed treatment ≥4 weeks prior to registration and discontinue steroids ≥2 weeks before beginning study and remained symptom-free.	Participants must have received at least 2 lines of hormonal therapy and can receive up to 2 lines of chemotherapy.
Erlotinib (BMS-690514) + Letrozole	NCT01068704	Phase II, completed	Participants had HR + MBCB but symptomatic BM were excluded.	HER2+/− were accepted and participants had disease progression despite treatment with tamoxifen, anastrozole, or exemestane.
Esterified Estrogens	NCT00131924	Phase II, terminated (poor accrual)	Participants must have HR+ MBCB where BM are included provided participants received previous treatment for BM, are stable, and BM are not the only site of metastasis.	Participants' disease must have progressed following treatment with at least 2 prior endocrine therapies.

Compound	Trial	Phase and Status	Parameters	Comment
Estradiol + Exemestane	NCT01385280	Pilot study, completed	Participants must have HR+ MBCB and treated CNS metastases are included.	Participants must have had prior AI therapy.
Everolimus + Letrozole + Trastuzumab	NCT02152943	Phase I, currently recruiting	Participants must have HR+/HER2+ MBCB where CNS metastases are included if previously treated and stable for 3 weeks and off steroids and anticonvulsants.	Leptomeningeal disease is excluded.
Everolimus + Anti-Estrogen	NCT02291913	Phase II, ongoing but not recruiting	Participants have HR+/HER2− MBCB where BM are eligible if treated ≥2 weeks before study and not currently receiving enzyme inducing anti-epileptic drugs or steroids.	
Everolimus	NCT02387099 (Desiree)	Phase II, currently recruiting	Participants with HR+/HER2− MBCB who do not have symptomatic visceral metastases. Brain metastases are included if previously treated by surgery and/or radiotherapy.	
Everolimus + AI	NCT02511639 (MAIN-A)	Phase 3, currently recruiting	Participants have HR+/HER2− MBCB where symptomatic CNS metastases are excluded.	Participants must have received 1 line of prior chemotherapy.
Everolimus + Hormone Therapy	NCT02269670	Phase II, ongoing but not recruiting	Participants have HR+/HER2− MBCB where uncontrolled CNS metastases are excluded.	Participants demonstrate disease progression on everolimus and exemestane combination.
Everolimus + Letrozole + Leuprorelin	NCT02344550 (LEO)	Phase II, currently recruiting	Participants have HR+/HER2− MBCB, where symptomatic BM are excluded.	Must have progressive disease after treatment with tamoxifen +/− GnRH agonist.
Exemestane + Sunitinib	NCT00905021 (EXTENT)	Phase I & II, terminated (sponsor withdrew support)	Participants with HR+ MBCB and CNS metastases is allowed if stable for >3 months.	HER2+ is allowed but must have failed treatment with trastuzumab.
Fulvestrant + Everolimus + Exemestane	NCT02404051 (FEVEX)	Phase 3, currently recruiting	Participants have HR+/HER2− MBCB, where symptomatic CNS metastases are excluded.	

Compound	Trial	Phase and Status	Parameters	Comment
Fulvestrant +/− Ganetespib	NCT01560416	Phase II, ongoing but not recruiting	Participants have HR+/HER2− MBCB, where untreated or progressive brain metastases are excluded.	
Fulvestrant + MK-0646 + Dasatinib	NCT00903006	Phase I & II, terminated (low accrual)	Participants have HR+/HER2− MBCB, where active or untreated BM were excluded.	
Fulvestrant +/− Lapatinib	NCT00390455	Phase 3, ongoing but not recruiting	Participants have HR+/HER2+/− MBCB and asymptomatic CNS metastases or BM that is >3 months past treatment are eligible.	Participants must have received prior treatment with 1–2 endocrine therapies and third-generation AI.
G1T38 + Fulvestrant	NCT02983071	Phase I & II, currently recruiting	Participants have HR+/HER2− MBCB, where active, uncontrolled, symptomatic CNS metastases are excluded.	Participants' disease must have progressed on or after treatment with an AI or tamoxifen.
GDC-0077 + Fulvestrant + Letrozole + Palbociclib	NCT03006172	Phase I, currently recruiting	Participants have HR+/HER2− MBCB, where active, untreated CNS metastases are excluded.	Participants have PIK3CA mutation.
GDC-0810 + Letrozole and/or LHRH Agonist	NCT01823835	Phase I & II, ongoing but not recruiting	Participants have HR+/HER2− MBCB, where untreated, symptomatic CNS metastases are excluded.	Participants' disease must have progressed after ≥6 months of hormonal therapy.
IMP321 + Paclitaxel	NCT02614833 (AIPAC)	Phase II, currently recruiting	Participants have HR+ MBCB but symptomatic CNS metastases are excluded.	
Irinotecan + Temozolomide	NCT00617539	Phase II, completed	MBCB with BM that has progressed following treatment.	Hormone receptor status not specified.
Lapatinib	NCT00759642	Phase II, ongoing but not recruiting	Participants have HR+/HER2− MBCB, where CNS metastases are eligible if >3 months from treatment and asymptomatic.	Must have disease progression on or after treatment with AI and/or fulvestrant.
Lenvatinib + Letrozole	NCT02562118	Phase I & II, currently recruiting	Participants have HR+ BC but symptomatic BM are excluded.	
Letrozole + Celecoxib	NCT00101062	Phase II, terminated (study drug unavailable)	Participants had HR + MBCB, where BM were included if controlled by radiotherapy or	

Compound	Trial	Phase and Status	Parameters	Comment
			surgical resection ≥6 months before study.	
MK-2206 + Exemestane + Goserelin	NCT01240928	Phase I, withdrawn (funding not available)	Participants had HR + BC and CNS metastases were included if stable for >1 month prior to study.	
MK-2206 + Exemestane + Goserelin	NCT01240941	Phase II, withdrawn (funding not available)	Participants had HR + BC and CNS metastases were included if stable for >1 month prior to study.	
Paclitaxel + Pictilisib	NCT01740336 (PEGGY)	Phase II, completed	Participants had HR +/HER2− MBCB but untreated or active CNS metastases were excluded.	
Palbociclib + Anti-HER2 Therapy + Endocrine Therapy	NCT02947685 (PATINA)	Phase 3, currently recruiting	Participants have HR+/HER2+ MBCB and CNS metastases are eligible if no progression after CNS directed therapy and >3 weeks between radiotherapy and study start.	
Palbociclib + Tamoxifen	NCT02668666	Phase II, currently recruiting	Participants have HR+ MBCB and BM are eligible after tumors have been treated with resection and/or radiotherapy and neurologically stable >1 month off steroids.	
Palbociclib + Letrozole or Fulvestrant	NCT02692755 (PALINA)	Phase II & 3, currently recruiting	Participants have HR+/HER2− MBCB, where uncontrolled or symptomatic BM are excluded.	Participants must self-identify as black, African, or African-American.
Palbociclib + Everolimus + Exemestane	NCT02871791	Phase I & II, currently recruiting	Participants have HR+/HER2− MBCB and CNS metastases are included if treated by surgery or radiotherapy with >3 months of stable disease, not requiring steroids or enzyme inducing anti-epileptic medications.	
Palbociclib + Fulvestrant	NCT01942135 (PALOMA-3)	Phase 3, ongoing but not recruiting	Participants have HR+/HER2− MBCB, where uncontrolled or symptomatic CNS metastases are excluded.	

Compound	Trial	Phase and Status	Parameters	Comment
Palbociclib + Letrozole	NCT02600923	Phase 3, currently recruiting	Participants have HR+/HER2− MBCB and treated, clinically stable BM are permitted.	
Palbociclib + Fulvestrant	NCT02738866	Phase II, currently recruiting	Participants have HR+/HER2− MBCB and CNS metastases are allowed if treated and stable.	Disease progression on prior treatment with palbociclib + AI.
Palbociclib + Exemestane + Goserelin	NCT02917005 (FATIMA)	Phase II, not yet open for recruitment	Participants have HR+/HER2− MBCB, where uncontrolled CNS metastases are excluded.	Women must be premenopausal.
Palbociclib + AI or Fulvestrant	NCT02894398 (INGE-B)	Phase II, currently recruiting	Participants have HR+/HER2− MBCB, where known non-irradiated CNS metastases are excluded.	
Palbociclib + Bazedoxifene	NCT02448771	Phase I & II, currently recruiting	Participants have HR+/HER2− MBCB and treated BM not requiring steroids are eligible.	
Palbociclib + Fulvestrant or Tamoxifen	NCT02384239	Phase II, currently recruiting	Participants have HR+/HER2− MBCB and CNS metastases are eligible if definitively treated by radiotherapy or surgery, are stable, and off steroids and anticonvulsants >4 weeks before beginning study.	
Palbociclib + Exemestane + Leuprolide Acetate	NCT02592746	Phase II, currently recruiting	Participants have HR+/HER2− MBCB and treated and stable BM are included.	Participant must be premenopausal.
Palbociclib + Taselisib or Pictilisib	NCT02389842 (PIPA)	Phase I, status unknown	Participants have HR+ MBCB that can be HER2+/− and untreated or active CNS metastases are excluded.	HR+ must have progressed on ≥1 prior endocrine therapy; PIK3CA must have progressed on ≥1 prior endocrine or chemotherapy.
Pembrolizumab (MK-3475) + Doxorubicin or Anti-Estrogen Therapy	NCT02648477	Phase II, currently recruiting	Participants have HR+/HER2− or triple-negative MBCB and CNS metastases may participate if stable and not using steroids >7 days before trial.	
Pictilisib (GDC-0941) or GDC-0980 + Fulvestrant	NCT01437566	Phase II, completed	Participants have HR+/HER2− MBCB where	Disease progression on or

Compound	Trial	Phase and Status	Parameters	Comment
			untreated or active CNS metastases are excluded.	after treatment with an AI.
Ribociclib (LEE011) + Letrozole	NCT03096847	Phase 3, currently recruiting	Participants have HR+/HER2− MBCB and CNS metastases are eligible if prior therapy is completed ≥28 days before study, CNS tumors are stable, and patient is not using steroids or enzyme inducing anti-epileptic medications.	
Ribociclib + Fulvestrant	NCT02422615 (MONALEESA-3)	Phase 3, ongoing but not recruiting	Participants have HR+/HER2− MBCB and CNS metastases are eligible if prior treatment completed >4 weeks before study, stable, and not taking steroids or enzyme inducing anti-epileptic medications.	
Ribociclib + PDR001 +/− Fulvestrant	NCT03294694	Phase I, not yet open for recruitment	Participants have HR+/HER2− MBCB and CNS metastases are included if prior treatment completed >4 weeks before study, stable, and not using steroids or enzyme inducing anti-epileptic medications.	Study includes ovarian cancer.
Ribociclib + Fulvestrant	NCT02632045	Phase II, currently recruiting	Participants have HR+/HER2− MBCB and CNS metastases are eligible if definitive treatment and steroids are completed >4 weeks before study.	Participants must have disease progression on prior AI or CDK 4/6 inhibitor.
Ribociclib + Letrozole + Alpelisib	NCT01872260	Phase I, currently recruiting	Participants have HR+/HER2− MBCB, where active CNS metastases are excluded.	
Ribociclib + Tamoxifen	NCT02586675 (TEEL Study)	Phase I, ongoing but not recruiting	Participants have HR+/HER2− MBCB but CNS metastases are excluded unless specific criteria are met.	
Seribantumab + Fulvestrant	NCT03241810 (SHERBOC)	Phase II, currently recruiting	Participants have HR+/HER2− MBCB, where uncontrolled CNS	

Compound	Trial	Phase and Status	Parameters	Comment
			metastases are excluded.	
Sonidegib (LDE225) + Buparlisib (BKM120)	NCT01576666	Phase I, completed	Participants have MBCB and CNS metastases are eligible if controlled, asymptomatic, and stable.	Study includes pancreatic adenocarcinoma, colorectal cancer, and glioblastoma multiforme.
Sorafenib (BAY 43-9006) + Capecitabine	NCT01234337	Phase 3, ongoing but not recruiting	Participants with HER2− MBCB but active brain metastasis is excluded.	Participants must have received up to 2 prior chemotherapy regimens one of which must include an anthracycline.
Taselisib (GDC-0032) +/− Fulvestrant or Letrozole	NCT01296555	Phase I & II, currently recruiting	Participants have HR+/HER2− MBCB, where active, untreated CNS metastases are excluded.	Study includes Non-Hodgkin's Lymphoma.
Taselisib + Fulvestrant	NCT02340221 (SANDPIPER)	Phase 3, currently recruiting	Participants must have HR+/HER2− MBCB, where active, untreated CNS metastases are excluded.	
Temozolomide + WBRT	NCT02133677	Phase II, status unknown	Participants must have BM from BC or lung cancer.	Hormone status not specified.
Temozolomide + Radiation	NCT00875355	Phase II, status unknown	Participants must have BM from BC.	Hormone status not specified.
Tucatinib + Palbociclib + Letrozole	NCT03054363	Phase I & II, not yet open for recruitment	Participants have HR+/HER2+ MBCB and CNS metastases are included if asymptomatic or previously treated and off steroids for >4 weeks before study.	
Voxtalisib (XL765; SAR245409) or Pilaralisib (XL147; SAR245408) + Letrozole	NCT01082068	Phase I & II, completed	Participants have HR+/HER2− MBCB, where untreated, symptomatic, or progressive BM are excluded.	Disease is refractory to nonsteroidal AI.
Xentuzumab (BI 836845) + Abemaciclib +/− Hormonal Therapy	NCT03099174	Phase I, currently recruiting	Participants have HR+/HER2− MBCB and CNS metastases are eligible if treated and stable, off steroids and anticonvulsants >4 weeks.	Study includes 1 cohort of non-small cell lung cancer.

MBCB: metastatic breast cancer.

Table 3

Systemic chemotherapy trials in breast cancer brain metastases.

Compound	Combination	Outcomes	Summary
Cisplatin	Bevacizumab	In a Phase II trial of 35 patients pre-treated with bevacizumab and then given cisplatin and etoposide, 25 patients (77%) achieved a response rate. [91]	
	Etoposide	In a Phase II trial of 4 BCBM patients, 1 achieved a PR. [204] In 56 patients treated with the combination, 7 achieved CR, 14 PR, 12 did not change, 16 progressed, and 8 were not assessed, for an overall 38% response rate. [90]	Though it has poor CSF penetration, cisplatin can penetrate the blood-tumor barrier.
	Doxorubicin	Cisplatin, doxorubicin, methotrexate and 5-fluorouracil caused major toxicity with no improvement in 4 BCBM patients. [205]	
	Cyclophosphamide	6 patients achieved a PR in a Phase II trial of 15 patients with BCBM. [92]	
	Gemcitabine	In a trial of 15 BCBM, 4 of 6 were triple negative and achieved a response. [94]	
	Vinorelbine	In combination with a 30 Gy radiation schedule, a Phase II trial of 25 patients with cisplatin and vinorelbine resulted in 3 CR and 16 PR (76%). [93]	
Cyclophosphamide	Cisplatin	See **cisplatin**.	
	Methotrexate, 5-fluorouracil, vincristine, doxorubicin	Cyclophosphamide, methotrexate, and 5-fluorouracil were given to 20 patients with 13 attaining a positive response. [206] In 56 patients treated with cyclophosphamide, methotrexate, 5-fluorouracil and doxorobucin, PFS lengthened but no significant intracranial metastases-free interval. [207] In 27 of 52 patients (52%) with BCBM, response was achieved with cyclophosphamide, 5-fluorouracil and prednisone, 19 of 35 patients (54%) achieved response with cyclophosphamide, 5-fluorouracil, prednisone, methotrexate and vincristine, and 1 of 6 (17%) achieved response with cyclophosphamide and doxorubicin. [208]	
Doxorubicin	Cisplatin	See **cisplatin**.	
	Cyclophosphamide	See **cyclophosphamide**.	
	Topotecan, ifosfamide	5 BCBM patients treated with the triple combination, with progressive disease occurring 2 of 5. [209]	
	Teniposide, lomustine	8 patients were treated with this triple therapy, 5 showed improvement and symptom regression. [210]	
Eribulin		In one patient, eribulin was initiated as fifth-line therapy. Response was seen after one month, but ultimately the patient succumbed. [211] In three heavily treated patients, eribulin was found to be beneficial. [66] With concurrent whole-brain radiation therapy, eribulin regressed two brain metastases. [212]	
5-fluorouracil	Cisplatin	See **cisplatin**.	Though it can cross the blood-brain and blood-tumor barrier, 5-fluorouracil is not used as monotherapy, always as a combination agent. [213]
	Cyclophosphamide	See **cyclophosphamide**.	
Gemcitabine	Cisplatin	See **cisplatin**.	
	Vinorelbine	In a Phase II trial of 3 evaluated BCBM patients, 1 had PR while 2 remained stable. 2 patients had leptomeningeal involvement. [214]	

Compound	Combination	Outcomes	Summary
Irinotecan	Temozolomide	The combination was studied in NCT00617539, but results are not posted or published.	Irinotecan is not typically used in brain metastases treatment, but may find utility in combination with newer treatment modalities.
	Iniparib	Of 34 evaluatable patients in a Phase II trial, 4 (12%) achieved a CR, 13 (41%) achieved stable disease state, for a total of 27% achieving a clinical benefit. [215]	
Paclitaxel		Of 152 metastatic breast cancer patients, 78 (51%) responded to paclitaxel while 6 (4%) developed progression. [216]	The brain is considered a “sanctuary site” from paclitaxel, due to its low brain and CSF concentrations.
	Bevacizumab	Of 4 patients treated with the combination, 1 achieved CR and 3 achieved PR. No patients showed progression. [217] 2 patients achieved PR, 2 achieved stable disease, and 1 progressed when given combination therapy. [218]	
Temozolomide			
	Vinorelbine	6 patients achieved a minor response, which unfortunately progressed. [219] In a Phase II trial of 11 BCBM patients, only 1 achieved a minor response, while others were grouped into stable or progressing disease. [220]	
Veliparib		In a 25 patient Phase I trial, in combination with whole brain radiation therapy, median survival was 7.7 months compared to a predicted 4.9 months. [221]	

Table 4
Completed clinical trials of HER2+ BCBM

Patients receiving HER2-targeted therapy have improvements in overall and progression-free survival. Despite poor intracranial penetration, trastuzumab alone or with emtansine have good outcomes compared to chemotherapy or placebo.

Compound	Combination	Outcomes	Summary
Trastuzumab		The registHER study found that HER2+ BCBM patients who received trastuzumab following CNS disease diagnosis (n=258) had a median survival of 17.5 months as opposed to patients who did not receive trastuzumab (n=119) having a median survival of 3.7 months.	
Lapatinib	Capcitabine	HER2+ BCBM patients treated with LC combination (n=30) had a median OS of 27.9 months compared to patients treated with trastuzumab beyond brain progression only (n=23) having a median OS of 16.7 months. In the single-group phase 2 LANDSCAPE study, 29 of 44 HER2+ BCBM patients (65.9%) had an objective CNS response to LC combination treatment. HER2+ BCBM patients treated with LC combination (n=46) had a median survival of 19.1 months compared to patients treated with trastuzumab-based therapy (n=65) having a median OS of 12 months.	
Trastuzumab emtansine (T-DM1)		The phase 3 EMILIA study found that $HER2^+$ BCBM patients treated with T-DM1 (n=45) had a median OS of 26.8 months compared to patients who received LC combination treatment (n=50) having a median OS of 12.9 months. T-DM1 was shown to significantly decrease index lesion size (M1: from 1.6 cm to 0.8 cm) in one $HER2^+$ BCBM patient. Of 10 $HER2^+$ BCBM patients treated with T-DM1, 3 had partial remission, 2 had stable disease lasting for ≥ 6 months, 2 had stable disease for < 6 months, and 3 progressed. All 4 $HER2^+$ BCBM patients treated with T-DM1 had 30% or greater reduction in tumor size, and 1 was maintained on therapy for 16 months. T-DM1 was administered to 39 $HER2^+$ BCBM patients; median PFS was 6.1 months and one-year OS rate was 58%. The phase 3 TH3RESA trial found that $HER2^+$ BCBM patients who received T-DM1 (n=404) had a median OS of 22.7 months compared to patients who received treatment of physician's choice (TPC) (n=198) having a median OS of 15.8 months.	

OS: overall survival; PFS: progression-free survival.

Table 5
Upcoming clinical trials for HER2+ BCBM

The success of lapatinib, capecitabine, trastuzumab and its conjugation to emtansine, have led these agents to be backbone therapy in the majority of newly initiated or in-progress trials for patients with HER2+ BCBM.

Compound	Trial	Phase and Status	Parameters	Comment
T-DM1 + Sequential Brain RT	NCT02135159	1, complete.	No previous WBRT or leptomeningeal disease.	No study results posted.
Lapatinib + WBRT + Herceptin	NCT00470847	1, complete.	No previous WBRT or other concurrent hormonal or chemotherapy.	Median OS of 19 months.
Lapatinib + Temozolomide	NCT00614978	1, complete.	Steroids and previous trastuzumab allowed.	No study results posted.
ARRY-380 + Trastuzumab	NCT01921335	1, active, not recruiting.	No radiation or chemotherapy >14 days before enrollment, no seizure history.	No study results posted.
Pertuzumab + Trastuzumab	NCT02598427	1, Terminated in Feb 2018.	No seizures or WBRT, no seizure or neuropsychiatric history.	Intrathecal administration of antibodies.
T-DM1 + Metronomic Temozolomide	NCT03190967	1 and 2, recruiting	No WBRT or symptomatic brain metastases or cardiac issues.	For secondary prevention of $HER2^{+}$ BCBM following SRS
Afatinib + Vinorelbine	NCT01441596	2, complete	Previous HER2+ tyrosine kinase use other than lapatinib not allowed, chemotherapy discontinued at least 14 days prior to enrollment.	No OS benefit vs. TPC
Everolimus + Trastuzumab + Vinorelbine	NCT01305941	2, active, not recruiting	No prior mTOR inhibitors or cardiac history, stable on dexamethasone, >4 weeks after cranial surgery.	65% of 26 patients had stable disease with about 4 months to intracranial progression.
Lapatinib	NCT00263588	2, active, not recruiting	No neuropsychiatric or cerebral vascular diseases.	No study results posted.
Surgical Resection + Neratinib	NCT01494662	2, active, not recruiting	2 week washout of prior therapy and radiation, no concurrent hormonal therapy, no antiepileptic drugs.	49% had volumetric reduction, 24% had overall response rates with a 6 month progression-free survival and a 13.5 month median overall survival.
Palbocicib + Trastuzumab	NCT02774681	2, recruiting	Stable corticosteroid use, with no HER2+ therapy other than trastuzumab allowed.	No study results posted.
Lapatinib Ditosylate + SR or WBRT	NCT01622868	2, recruiting	No prior radiation and concurrent lapatinib therapy, cardiovascular issues.	No study results posted.
Tucatinib + Capecitabine + Trastuzumab	NCT02614794	2, recruiting	No lapatinib within 12 months, no neratinib or HER2+ agent or capecitabine prior.	No study results posted.
Cabozantinib + Trastuzumab	NCT02260531	2, recruiting	Previous c-Met use, seizure history, prior lapatinib use within 1 week of starting.	No study results posted.
T-DM1 (Kadcyla)	NCT03203616	2, not yet recruiting.	Must have >1 metastases, cannot have hormonal therapy within 14 days or trastuzumab within 21 days of enrollment.	

SR: stereotactic radiation; TPC: treatment of physician choice; WBRT: whole-brain radiation therapy.