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# Advances in the management of breast cancer brain metastases

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**Abstract**

The development of breast cancer (BC) brain metastases (BrM) is a common complication of advanced disease, occurring in up to half of the patients with advanced disease depending on the subtype. The management of BCBrM requires complex multidisciplinary care including local therapy, surgical resection and/or radiotherapy, palliative care, and carefully selected systemic therapies. Significant progress has been made in the human epidermal growth factor receptor 2-positive (HER2+) BCBrM population due to novel brain penetrable systemic therapies. Increased inclusion of patients with BCBrM in clinical trials using brain-penetrant systemic therapies recently led to the first FDA approval of a HER2-directed therapy specifically in the BCBrM population in the last year. Advances for the treatment of HR+/HER2– and TNBC BCBrM subgroups continue to evolve. In this review, we will discuss the diagnosis and multidisciplinary care of BCBrM. We focus on recent advances in neurosurgery, radiation therapy, and systemic treatment therapies with intracranial activity. We also provide an overview of the current clinical trial landscape for patients with BCBrM.

**Keywords**

brain metastases | breast cancer | stereotactic radiosurgery | surgical resection | systemic therapies

The development of breast cancer (BC) brain metastases (BrM) is a common complication of advanced disease, requiring complex and multidisciplinary medical management. Coordinated care, often including neuroradiology, neurosurgery, radiation oncology, medical oncology, and palliative care, leads to optimal outcomes. The incidence of breast cancer to brain metastases (BCBrM) varies by subtype, developing in approximately 1/2 of triple-negative breast cancer (TNBC), 1/3 of human epidermal growth factor receptor 2-positive (HER2+) BCs, and 14% of hormone receptor-positive (HR+)/HER2– disease.[1] Molecular subtypes, performance status, extracranial disease status, leptomeningeal metastasis, and number of lesions are all independent factors for the prognosis of patients with BCBrM.[2] Overall survival (OS) has improved in the HER2+ BCBrM population due to novel systemic therapies,[3] though progress for the HR+/HER2– and TNBC BCBrM subgroups has trailed behind.

Central nervous system (CNS)-directed therapies such as surgical resection and radiotherapy are the cornerstone of local treatment for BCBrM. Advances in modern radiation therapies including stereotactic radiosurgery (SRS) and a tendency to reserve whole-brain radiation therapy (WBRT) as salvage have improved cognition and quality of life for BCBrM patients. Several studies have shown that carefully selected systemic therapies, including endocrine therapies and HER2-targeted therapies, following CNS-directed therapy, improve survival for BCBrM patients.[4–6]

Despite major advances across subtypes in novel systemic treatments for advanced BC, progress for BCBrM patients has lagged behind due to suboptimal preclinical models of BCBrM, poor blood-brain barrier (BBB) penetration of therapies, lack of inclusion in clinical trials, and difficulty with standardization of CNS-specific clinical endpoints. In recent years, national guidance encouraging inclusion of BCBrM patients in early and late phase clinical trials has been a catalyst to improved systemic treatments and led to the first FDA indication of a drug regimen specifically including the HER2+ BCBrM population[3] in 2020. The development of new systemic therapies for metastatic BC with BBB penetration in concert with unprecedented inclusion in clinical trial design and standardization of BrM-specific clinical endpoints has led to an infused interest in developing novel therapeutic approaches for BCBrM. In this review, we discuss recent developments in local and systemic management as well as promising ongoing clinical trials specific to the BCBrM population.

## Diagnosis

### Optimal Imaging Modality

The sensitivity of magnetic resonance (MR) over computed tomography (CT) brain imaging in detecting BrM has clearly been demonstrated.[7] However, even with MRI, the specific protocol for image acquisition can impact the ability to detect and define BrM and thereby impact the decisions around treatment, the ability to effectively deliver treatment, and the ability to accurately evaluate response to treatment.[8] With the critical need for consistent, serial tumor measurement for reliable tumor response assessment to evaluate new therapeutic approaches for BrM, a multidisciplinary team generated a consensus protocol called the Brain Tumor Imaging Protocol-Brain Metastases[9] with the aim of providing guidance to standardize image acquisitions for the assessment of BrM across institutions. These consensus recommendations provide guidance for both 1.5T and 3T MR systems and provide a range from the "minimum standard" up to an "ideal" protocol. In the "minimum standard" protocol, the following pulse sequences are recommended: (i) parameter matched pre- and post-contrast inversion recovery (IR)-prepared, isotropic 3D T1-weighted gradient echo (IR-GRE); (ii) axial 2D T2-weighted turbo spin-echo acquired after injection of gadolinium-based contrast agent and before post-contrast 3D T1-weighted images; (iii) axial 2D or 3D T2-weighted fluid-attenuated IR; (iv) axial 2D, 3-directional diffusion-weighted images; and (v) post-contrast 2D T1-weighted spin-echo images for increased lesion conspicuity.

### Screening and Monitoring

Both the National Comprehensive Cancer Network (NCCN) and the American Society of Clinical Oncology (ASCO) recommend against routine screening for BrM in patients with BC.[10] The available evidence supports this recommendation, with only a 1.3% 10-year cumulative incidence of CNS metastases as the first site of metastatic presentation among 9524 patients enrolled across International Breast Cancer Study Group clinical trials.[11] However, even in this study, Pestalozzi et al reported a significantly higher incidence among patients with high-risk tumors including high T-stage, node-positive, Grade 3, and HER2 and estrogen receptor (ER) negativity.

There are limited clinical studies investigating the role of screening studies for BrM in patients with advanced BC. Niwinska et al reported that after a single screening brain MRI, asymptomatic BrM were found in 11 of 32 (34%) patients with HER2+ metastatic BC.[12] It is well known that the incidence of BrM is substantially higher in subgroups including patients with advanced or metastatic HER2+ and TNBC. Consistent with other solid malignancies, presentation with symptomatic BrM is independently associated with adverse OS (hazard ratio, 1.58; 95% confidence interval [CI], 1.04–2.41; P 1/4.033), as shown in a large retrospective study of 557 patients with metastatic BC.[13] Given increasingly effective therapies and a potential for prolonged survival after a diagnosis of BCBrM, earlier detection via screening of asymptomatic BrM in advanced and metastatic HER2+ and TNBC should be studied from a perspective of quality of life as well as OS.[14,15] Several clinical trials are underway to understand the value of screening brain MRI in patients with metastatic BC (clinicaltrials.gov, Identifier: NCT04030507) (Table 1).

## Local Therapies

### The Role of Surgical Resection

With improved OS of patients with metastatic BC, including patients with BrM, there has been increased optimism and consideration of neurosurgical interventions. The primary indications for neurosurgical resection remain similar to other solid tumor histologies, including larger-sized metastases that may benefit from combined surgery and radiation treatment,[16] relief of mass effect to facilitate improvement in functional status, and to facilitate tapering of corticosteroids. Among BC patients with a prolonged disease-free interval, histological confirmation of a brain lesion may be required. Additionally, surgery can enable definitive diagnosis of truly progressive disease vs radiation necrosis following treatment with CNS-directed radiation therapy.

In addition to these more traditional considerations, growing data support molecular evolution of BC and resulting disparate molecular phenotypes in metastatic sites compared to the primary BC. Recent studies have reported receptor expression discordance between primary BC and BrM in 36%–43% of cases for ER (16%–17%), PR (23%–25%), and HER2 (10%–13%), resulting in a subtype switch between the primary and BrM in 23%–36% of cases.[17–20] Compared to primary tumors, BCBrM can demonstrate a loss of ER (11%–15%) or PR (15%–23%), a gain of either HR (25%) or gain of HER2 (9%–15%).[17–20] Additionally, when comparing BrM to extracranial metastases, the discordance rate was even larger (64%) than for primary vs BCBrM (36%).[19,20] Furthermore, these data indicate that these molecular changes between the primary tumor and BCBrM

**Table 1.** Recruiting or Not Yet Recruiting Clinical Trials in Subtype-Independent Breast Cancer Brain Metastases, Including Local Therapy Approaches

| NCT # (Phase) | Trial Name | Population | Intervention | Primary Endpoint |
|---|---|---|---|---|
| 04543188 (I) | FIH Study of PF-07284890 in Participants With BRAF V600 Mutant Solid Tumors With and Without Brain Involvement | • BRAF V600 mutation in tumor tissue or blood<br>• BrM not requiring immediate local intervention<br>• Symptomatic or asymptomatic BrM | • PF-07284890 alone or combined with binimetinib | • DLTs<br>• Treatment-emergent AEs<br>• Dose interruptions/modifications<br>• Overall response |
| 03608020 (I/II) | A Safety Lead-In/Randomized Phase 2 Study of BMX-001 as a Therapeutic Agent for Treatment of Cancer Patients with Multiple Brain Metastases Undergoing Whole-Brain Radiotherapy | • >5 contrast-enhancing lesions, with ≥1 lesion >0.5 cm, never previously treated with SRS and/or surgical resection<br>• Plan to be treated with WBRT to 30 Gy in 10 fractions | • BMX-001 with WBRT vs<br>• WBRT only | • Safety, tolerability of WBRT + BMX-001 (grade 4/5 drug-related AEs)<br>• Neurocognition (HVLT-R, TMT A&B, COWA) |
| 04789668 (I/II) | Phase I/II Trial of BINTRAFUSP ALFA (M7824) and Pimasertib for Treatment of Intracranial Metastases | • ≥1 brain lesion ≥0.5 cm and <3.0 cm<br>• Prior SRS on up to 3 lesions | • Bintrafusp Alfa with pimasertib | • CBR<br>• DLTs<br>• RP2D<br>• Time to intracranial progression<br>• OS |
| 03994796 (II) | Genomically Guided Treatment Trial in Brain Metastases (Alliance A071701) | • Clinically actionable alteration in NTRK, ROS1, CDK, or PI3K pathway<br>• At least 1 prior HER2-directed therapy in metastatic setting | • Palbociclib or GDC-0084 or entrectinib dependent on the presence of gene mutation | • ORR in the brain (RANO-BM) |
| 03449238 (II) | Pembrolizumab and Stereotactic Radiosurgery (SRS) of Selected Brain Metastases in Breast Cancer Patients | • ≥2 untreated BrM >5 mm eligible for SRS | • Pembrolizumab | • Tumor response (RECIST1.1)<br>• Abscopal response correlation<br>• OS |
| 04030507 (II) | Screening Magnetic Resonance Imaging of the Brain in Patients With Metastatic Breast Cancer Managed With First-/Second-Line Chemotherapy or Inflammatory Breast Cancer Managed With Definitive Intent: A Prospective Study | • Breast cancer with pathologic assessment of ER, PR, and HER2 status<br>• Extracranial, distant metastases; unresectable, locally recurrent BC, or inflammatory BC | • Initial screening brain MRI | • Neurologic quality of life at 12 months<br>• Incidence of symptomatic BrM<br>• Incidence of BrM |
| 03741673 (III) | Preoperative SRS or postoperative SRS in Treating Cancer Patients With Brain Metastases | • Brain lesion ≤4 cm for single fraction, ≤7 cm for multi-fraction SRS<br>• SRS candidate within ±30 days of surgical resection | • Preoperative SRS vs<br>• Postoperative SRS | • Leptomeningeal disease-free rate |
| 04114981 (III) | Single Fraction Stereotactic Radiosurgery Compared With Fractionated Stereotactic Radiosurgery in Treating Patients With Resected Metastatic Brain Disease | • 0–3 unresected BrM<br>• Unresected lesions <4.0 cm<br>• Resected lesion ≥2 cm preoperatively<br>• Resection cavity <5.0 cm | • Single Fraction SRS vs<br>• Fractionated SRS | • Surgical bed recurrence-free survival |
| 03550391 (III) | Stereotactic Radiosurgery Compared with Hippocampal-Avoidant Whole-Brain Radiotherapy (HA-WBRT) Plus Memantine for 5–15 Brain Metastases | • 5–15 BrM<br>• Largest BrM <2.5 cm | • HA-WBRT with Memantine vs<br>• SRS | • OS<br>• Neurocognitive PFS |

**Table 1.** Continued

| NCT # (Phase) | Trial Name | Population | Intervention | Primary Endpoint |
|---|---|---|---|---|
| 04246879 (N/A) | Diagnostic Accuracy of Delayed MRI Contrast Enhancement Characteristics and Radiation Necrosis Following Stereotactic Radiosurgery (SRS) for Brain Metastases | • ≥1 BrM previously treated with SRS<br>• Radiographic progression on post-SRS imaging<br>• Candidate for LITT procedure | • One additional delayed MRI sequence | • Number of positive MRI sequences<br>• Positive or negative tumor biopsies |

AE, adverse event; BC, breast cancer; BrM, brain metastasis; CBR, clinical benefit rate; DLT, dose-limiting toxicity; LITT, laser interstitial thermal therapy; RP2D, recommended phase 2 dosing; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; SRS, stereotactic radiosurgery; (HA-)WBRT, (hippocampal avoidance) whole-brain radiation therapy.

may impact clinical outcomes, with loss of HRs generally correlating with worse survival.[18–20] Thus, an additional benefit of neurosurgical resection is to confirm the molecular characteristics of the BrM specifically to guide personalized therapy, which is the focus of ongoing clinical trials (clinicaltrials.gov, Identifier: NCT03994796) (Table 1).

### Optimal Radiation Therapy Approaches

With advances in systemic therapy to achieve successful extracranial tumor control, the need for more sustained control of intracranial metastatic disease with increased consideration for long-term toxicities has grown substantially. This is reflected in the more recent phase III trials in BrM that have focused on the primary outcome of neurocognitive preservation and techniques of radiotherapy that aim to limit neurocognitive toxicity while achieving tumor control, including hippocampal avoidance whole-brain radiotherapy (HA-WBRT) and SRS for a growing number of metastases under consideration.[21–23] The evidence suggests that for limited disease in the brain, the preferred approach is radiosurgery with consideration of combined radiosurgery and surgery for larger (ie, >2.5 cm) metastases based on the randomized trial by Mahajan et al.[16] Consideration of radiosurgery pre- vs postoperatively is currently under clinical trial investigation (clinicaltrials.gov, Identifier: NCT03741673) (Table 1). In the postoperative setting, there are ongoing trials to determine whether single fraction or multi-fraction radiosurgery will result in better tumor control and less toxicities (clinicaltrials.gov, Identifier: NCT04114981) (Table 1). In the setting of greater than 4 metastases, there are ongoing randomized trials to definitely determine whether radiosurgery would still result in better overall clinical outcomes compared with HA-WBRT in terms of treatment benefit relative to toxicity (clinicaltrials.gov, Identifier: NCT03550391) (Table 1). Of note, these trials are not specifically focused on BCBrM, and there is clearly an opportunity to explore the optimal combination of radiosurgery and systemic therapy approaches to minimize toxicity and maximize intracranial tumor control.

In terms of combined systemic therapy and radiation, prior studies have failed to demonstrate the benefit of combining WBRT with concurrent systemic agents including temozolomide[24] and lapatinib. The results of the randomized phase II trial of WBRT with or without concurrent lapatinib (RTOG 1119), reported at the 2020 Society for Neuro-Oncology Virtual Meeting, revealed that while concurrent lapatinib improved the 4-week response rate, it did not improve the 12-week complete response rate, which was the primary endpoint of the trial.[25] After limited toxicity in a phase I study of veliparib in combination with WBRT for BrM, with a large proportion of enrolled patients with BC,[26] there is an ongoing phase IIb randomized, controlled trial to investigate whether there is a benefit (clinicaltrials.gov, Identifier: NCT01657799) in non–small-cell lung cancer; however, BCBrM has not been evaluated. A recent systematic review has reported that the combination of lapatinib and SRS in patients with HER2+ BCBrM resulted in better local control (HR 0.47 [0.33,0.66], $P = .0001$) and survival.[27] Given the growing role of SRS in the management of BCBrM, further studies of the combination of SRS with novel agents are needed to guide optimized combination therapies moving forward.[28]

## Systemic Therapies for BCBrM

### HR+, HER2− BCBrM

Endocrine therapies such as selective estrogen receptor modulators (SERMs), aromatase inhibitors, and selective estrogen receptor downregulators (SERDs) are the backbone of early line treatment for metastatic HR+/HER2− BC and have limited single-agent efficacy in BCBrM. Extensive clinical research investigating novel SERMs and SERDs is underway,[29] including those with possible BBB penetration such as elacestrant.[30] In the last decade, the addition of inhibitors of cyclin-dependent kinases CDK4 and CDK6 (abemaciclib, palbociclib, and ribociclib) to endocrine therapy backbones has improved both progression-free survival (PFS) and OS in both endocrine sensitive and resistant populations and is standard of care. The majority of the phase III clinical trials leading to approval of these agents excluded BCBrM patients.[31] A phase II, multi-cohort study (clinicaltrials.gov, Identifier: NCT02308020) investigated the intracranial efficacy of abemaciclib 200 mg twice daily as monotherapy or with

endocrine therapy in patients with untreated or treated, but progressive, BCBrM. Cohort A ($n$ = 58) included HR+/HER2– BCBrM patients showing a confirmed intracranial overall response rate (ORR) of 5.2% (95% CI, 0.0%–10.9%) and an intracranial disease control rate of 65.5% (95% CI, 53.3%–77.7%).[32] Cohort D included 9 patients with HR+/HER2– BrM undergoing standard-of-care neurosurgical resection. Pharmacokinetics of these BrM demonstrated therapeutic concentrations of total active abemaciclib analytes which were 96- (CDK4) and 19-fold (CDK6) above in vitro $IC_{50}$. Due to the established clinical benefit and observed BBB penetration, abemaciclib is currently the preferred CDK4/6 inhibitor for HR+/HER2– BCBrM without prior exposure to CDK4/6 inhibition. A study evaluating the intracranial efficacy of elacestrant and abemaciclib in HR+/HER2– BCBrM is currently underway (clinicaltrials.gov, Identifier: NCT04791384) (Table 2).

Recent data suggest *PIK3CA*-activating mutations, found in up to 40% of patients with HR+/HER2– advanced BC, may be associated with an increased risk of BCBrM.[33] A small case series suggests potential efficacy of the *PIK3CA* inhibitor, alpelisib, in HR+/HER2– BCBrM.[34] As discussed above, studies suggest that molecular alterations found within BCBrM are divergent from matching primary and extracranial metastasis tumor specimens. Enrichment in PI3K/AKT/mTOR, CDK, and HER2/EGFR pathway alterations can be found in BrM.[35] More research is needed to understand the optimal methods of targeting genomic alterations in BCBrM and is currently underway (clinicaltrials.gov, Identifier: NCT03994796) (Table 1).

For HR+/HER2– BCBrM patients with endocrine and/or CDK4/6 resistance, single-agent chemotherapy with an agent with known activity against CNS metastases is recommended. Agents with some evidence of intracranial activity include capecitabine, platinums, and doxorubicin.[36] Early phase trials of liposomal irinotecan have shown promise in heavily pretreated HR+/HER2– metastatic BC in patients with and without BrM[37]; further studies of intracranial efficacy are underway (clinicaltrials.gov, Identifier: NCT03328884) (Table 3).

## HER2+ BCBrM

First-line treatment of HER2+ metastatic BC includes taxane-based chemotherapy added to monoclonal antibodies (mAbs) that target and inhibit HER2, trastuzumab, and pertuzumab, with the addition of endocrine therapy for HR+ patients. The addition of pertuzumab to taxane/trastuzumab has increased time to BCBrM development in the first line and has improved OS in patients who progress and develop BCBrM.[38] Taxane, trastuzumab, and pertuzumab remain the first-line treatment for patients with stable BrM. High-dose trastuzumab with pertuzumab has been studied in the phase II PATRICIA study in patients with progressive HER2+ BCBrM despite prior radiotherapy. There was a modest intracranial ORR of 11% with a clinical benefit rate at 6 months of 51%.[39]

Ado-trastuzumab emtansine (T-DM1), an antibody–drug conjugate (ADC) combining the HER2-targeting mAb with a microtubule-inhibiting drug, was until recently the standard-of-care second-line treatment for HER2+ metastatic BC due to its superiority over capecitabine/lapatinib (a tyrosine kinase inhibitor of HER1 and HER2) in the EMILIA clinical trial.[40] Patients with stable and treated baseline BCBrM were included in this clinical trial and derived a significant improvement in OS in the T-DM1 arm compared to the capecitabine/lapatinib arm [hazard ratio (HR) = 0.38; $P$ = .008; median, 26.8 vs 12.9 months].[41] In the BCBrM cohort of patients in the phase IIIb KAMILLA study, the intracranial response and clinical benefit rates were 21.4% and 42.9%, respectively, illustrating intracranial response to single-agent T-DM1.[42] However, recent results from DESTINY-Breast03 with trastuzumab deruxtecan (T-DXd) have led to a paradigm shift.

T-DXd is a novel ADC comprised of a HER2-monoclonal antibody resembling trastuzumab, a cleavable tetrapeptide-based linker, and a cytotoxic topoisomerase I inhibitor payload. In the DESTINY-Breast03 intention-to-treat population, median PFS by investigator assessment was 25.1 months with T-DXd and 7.2 months with T-DM1 (HR = 0.2649; P = $6.5 \times 10^{-24}$). Nearly a quarter of the patients in DESTINY-Breast03 had stable BrM, and subgroup analysis in these patients reported a major PFS benefit of T-DXd over T-DM1 (HR = 0.3796, range 0.2267–0.6357).[43] T-DXd is the new standard-of-care therapy in second-line HER2+ BC, including patients with stable BrM (Figure 1). The efficacy of T-DXd in untreated or treated/progressive BrMs is unknown. For patients with treated/progressive brain metastases, we prefer tucatinib/trastuzumab/capecitabine in the second-line based on the benefits in this specific population seen in the HER2CLIMB clinical trial which is discussed below (Figure 1). Efficacy of T-DM1 after T-DXd is unknown, though can be considered in the third-line and beyond.

In the third-line and beyond, we have several options with clear evidence of intracranial efficacy in the treatment of HER2+ BCBrM, though none have been studied after T-DXd. Tucatinib is an oral, potent, HER2-specific reversible tyrosine kinase inhibitor that is capable of crossing the BBB. Neratinib is an oral, irreversible, brain-permeable tyrosine kinase inhibitor with activity against HER1, HER2, and HER4. Tucatinib/trastuzumab/capecitabine, neratinib/capecitabine, and T-DM1 have shown impressive results for patients with HER2+ BCBrM. Our choice of sequencing between neratinib/capecitabine, tucatinib/trastuzumab/capecitabine, and T-DM1 is generally dependent on stable vs progressive nature of BCBrM, prior systemic treatments, visceral disease status, and diverse toxicity profiles. A comparison of the characteristics of HER2-targeting agents used to treat BCBrM is provided in Table 4.

The most robust data for the treatment of active HER2+ BCBrM at this time are with tucatinib, capecitabine, and trastuzumab.[49] The randomized, multicenter, international, HER2CLIMB clinical trial treated patients with HER2+ metastatic BC with trastuzumab/capecitabine plus the addition of tucatinib or placebo. All patients had prior trastuzumab, pertuzumab, and T-DM1. Almost half (47%) of the patients had stable untreated, stable treated, or treated/progressive BCBrM,[3] a novel inclusion for a large clinical trial. The addition of tucatinib improved both PFS and OS in the intention-to-treat and BCBrM population.

**Table 2.** Recruiting or Not Yet Recruiting Clinical Trials in HR+ and/or HER2+ Breast Cancer Brain Metastases

| NCT # (Phase) | Trial Name | Population | Intervention | Primary Endpoint |
|---|---|---|---|---|
| 02442297 (I) | Phase I Study of Intracranial Injection of T Cells Expressing HER2-Specific Chimeric Antigen Receptors (CAR) in Subjects With HER2-Positive Tumors of the Central Nervous System (iCAR) | • HER2+ solid tumor metastatic to the CNS | • HHER2-CAR T cells via intraventricular administration | • HDLTs incidence |
| 03696030 (I) | HER2-CAR T Cells in Treating Patients With Recurrent Brain or Leptomeningeal Metastases | • Treated, recurrent, or untreated BrM<br>• HER2+ cancer | • HER2 chimeric antigen receptor T-cell (HER2 CAR-T) cells | • Incidence of DLTs<br>• Treatment-related AEs (CTCAE v5.0) |
| 04487236 (I) | Trial of ZN-A-1041 Enteric Capsules in Patients With HER2-Positive Advanced Solid Tumors | Phase Ic:<br>• ≥1 measurable BrM<br>• No immediate local treatment required | • ZN-A-1041 and capecitabine | • Safety of ZN-A-1041 with capecitabine at RP2D |
| 03190967 (I/II) | T-DM1 Alone vs T-DM1 and Metronomic Temozolomide in Secondary Prevention of HER2-Positive Breast Cancer Brain Metastases Following Stereotactic Radiosurgery | Phase I:<br>• Any number of BrM treated with SRS/WBRT<br>Phase II:<br>• ≤10 BrM treated with SRS and/or resection | • Phase I: T-DM1 + temozolomide<br>• Phase II: randomization T-DM1 ± temozolomide | • MTD of Temozolomide with T-DM1<br>• mPFS |
| 04791384 (Ib/II) | Multicenter Open-Label Phase Ib/II Trial of Abemaciclib and Elacestrant in Patients With Brain Metastasis Due to HR+/HER2– Breast Cancer | • HR+, HER2– breast cancer<br>• ≥1 brain lesion measuring ≥10 mm or previously irradiated lesion increased in size by ≥5 mm | • Abemaciclib and elacestrant | • AEs incidence and severity (CTCAE)<br>• Intracranial ORR<br>• CBR in brain (RANO-BM) |
| 01494662 (II) | A Phase II Trial of HKI-272 (Neratinib), Neratinib and Capecitabine, and Ado-Trastuzumab Emtansine for Patients With Human Epidermal Growth Factor Receptor 2 (HER2)-Positive Breast Cancer and Brain Metastases | • Cohort-dependent, either resectable BrM or not resectable | Different cohorts receiving:<br>• Neratinib alone<br>• Neratinib + capecitabine<br>• Neratinib + T-DM1 | • CNS ORR |
| 03765983 (II) | Phase II Trial of GDC-0084 in Combination With Trastuzumab for Patients With HER2-Positive Breast Cancer Brain Metastases | • ≥1 measurable CNS metastasis ≥10 mm<br>• Untreated, treated, or progressive CNS lesions | • Trastuzumab + GDC-0084 | • CNSORR (RANO-BM)<br>• Correlation of p-4EBP1 in brain tumor and response in PDX model |
| 03933982 (II) | Pyrotinib Plus Vinorelbine in Patients With Brain Metastases From HER2-positive Metastatic Breast Cancer: A Prospective, Single-Arm, Open-Label Study | • ≥1 CNS metastasis ≥1 cm<br>• Controlled CNS symptoms<br>• No previous WBRT | • Pyrotinib + vinorelbine | • ORR in CNS (RANO-BM) |
| 04303988 (II) | A Prospective, Single-Arm, Single-Center, Multi-Cohort Phase II Clinical Study of HER2-Positive and Triple-Negative Breast Cancer Brain Metastases | • HER2+ BC<br>• Previously received trastuzumab and taxanes<br>• ≥1 BrM ≥1.0 cm | • Pyrotinib with temozolomide | • CNS ORR (RANO-BM) |
| 04334330 (II) | Palbociclib, Trastuzumab, Lapatinib and Fulvestrant Treatment in Patients With Brain Metastasis From ER-Positive, HER2-Positive Breast Cancer | • ER+, HER2+ breast cancer<br>• ≥1 brain lesion measuring ≥10 mm | • Palbociclib, trastuzumab, lapatinib, and fulvestrant | • ORR in CNS (RANO-BM) |

**Table 2.** Continued

| NCT # (Phase) | Trial Name | Population | Intervention | Primary Endpoint |
|---|---|---|---|---|
| 04420598 (II) | DS-8201a for trEatment of aBc, BRain Mets, and Her2[+] Disease (DEBBRAH) | • ≥1 BrM ≥10 mm<br>• Non-progressing, asymptomatic, or new/progressing brain metastases | • Trastuzumab deruxtecan | • 16-week PFS<br>• CNS ORR |
| 04752059 (II) | Phase II Study of Trastuzumab-Deruxtecan (T-DX; DS-8201a) in HER2-Positive Breast Cancer Patients With Newly Diagnosed or Progressing Brain Metastases (TUXEDO-1) | • HER2+ breast cancer<br>• Newly diagnosed BrM or progressing after local therapy<br>• Measurable disease by RANO-BM | • Trastuzumab deruxtecan | • RR of BrM (RANO-BM) |

AE, adverse event; BrM, brain metastasis; CBR, clinical benefit rate; CNS, central nervous system; DLT, dose-limiting toxicity; MTD, maximum tolerated dose; RP2D, recommended phase 2 dosing; PFS, progression-free survival; RR, response rate; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

**Table 3.** Recruiting or Not Yet Recruiting Clinical Trials in HER2– and/or TNBC Breast Cancer Brain Metastases

| NCT # (Phase) | Trial Name | Population | Intervention | Primary Endpoint |
|---|---|---|---|---|
| 03328884 (II) | Multicenter Open-Label, Phase II Trial, to Evaluate the Efficacy and Safety of Nal-IRI for Progressing Brain Metastases in Patients With HER2-Negative Breast Cancer (the Phenomenal Study) | • HER2– BC<br>• New or progressive BrM following WBRT, SRS, and/or surgery<br>• ≥1 BrM ≥10 mm | • Irinotecan hydrochloride (nal-IRI) | • CNS ORR (RANO-BM) |
| 04303988 (II) | A Prospective, Single-Arm, Single-Center, Multi-Cohort Phase II Clinical Study of HER2-Positive and Triple-Negative Breast Cancer Brain Metastases | • TNBC<br>• No platinum previously used or has been used but platinum-sensitive<br>• ≥1 BrM ≥1.0 cm | • SHR-1316, bevacizumab, and cisplatin/carboplatin | • CNS ORR (RANO-BM) |
| 04348747 (II) | Dendritic Cell Vaccines Against Her2/Her3, Cytokine Modulation Regimen, and Pembrolizumab for the Treatment of Brain Metastasis From Triple-Negative Breast Cancer or HER2+ Breast Cancer | • TNBC<br>• ≥1 BrM ≥0.5 cm and <3.0 cm that is asymptomatic and does not require immediate local therapy | • Anti-HER2/HER3 dendritic cell vaccine with celecoxib, pembrolizumab, interferon α-2b, and rintatolimod | • Best overall CNS response (RANO-BM) |
| 04434560 (II) | A Phase II Trial of Surgery and Stereotactic Radiosurgery With Neoadjuvant Nivolumab and Ipilimumab in Patients With Surgically Resectable, Solid Tumor Brain Metastases | • TNBC<br>• 1–3 untreated BrM ≤4 cm<br>• ≥1 BrM resectable<br>• All BrM planned for SRS<br>• Plan for immunotherapy<br>• Asymptomatic/minimally symptomatic | • Nivolumab with ipilimumab | • Proportion of surgeries delayed/never occur<br>• Circulating T-cell proliferation |
| 04647916 (II) | A Phase II Trial of Sacituzumab Govitecan (IMMU-132) (NSC #820016) for Patients With HER2-Negative Breast Cancer and Brain Metastases | • HER2– BC<br>• ≥1 BrM ≥1 cm | • Sacituzumab govitecan | • ORR |
| 02448576 (III) | A Phase III Randomized Controlled Trial of Prophylactic Cranial Irradiation in Patients With Advanced Triple-Negative Breast Cancer Who Had a Response to First-Line Chemotherapy | • TNBC<br>• Response after 4–8 cycles of first-line chemotherapy | • Prophylactic cranial radiation (PCI)<br>vs<br>• Observation | • BrM-free survival |

AE, adverse event; BrM, brain metastasis; CNS, central nervous system; SRS, stereotactic radiosurgery; WBRT, whole-brain radiation therapy.

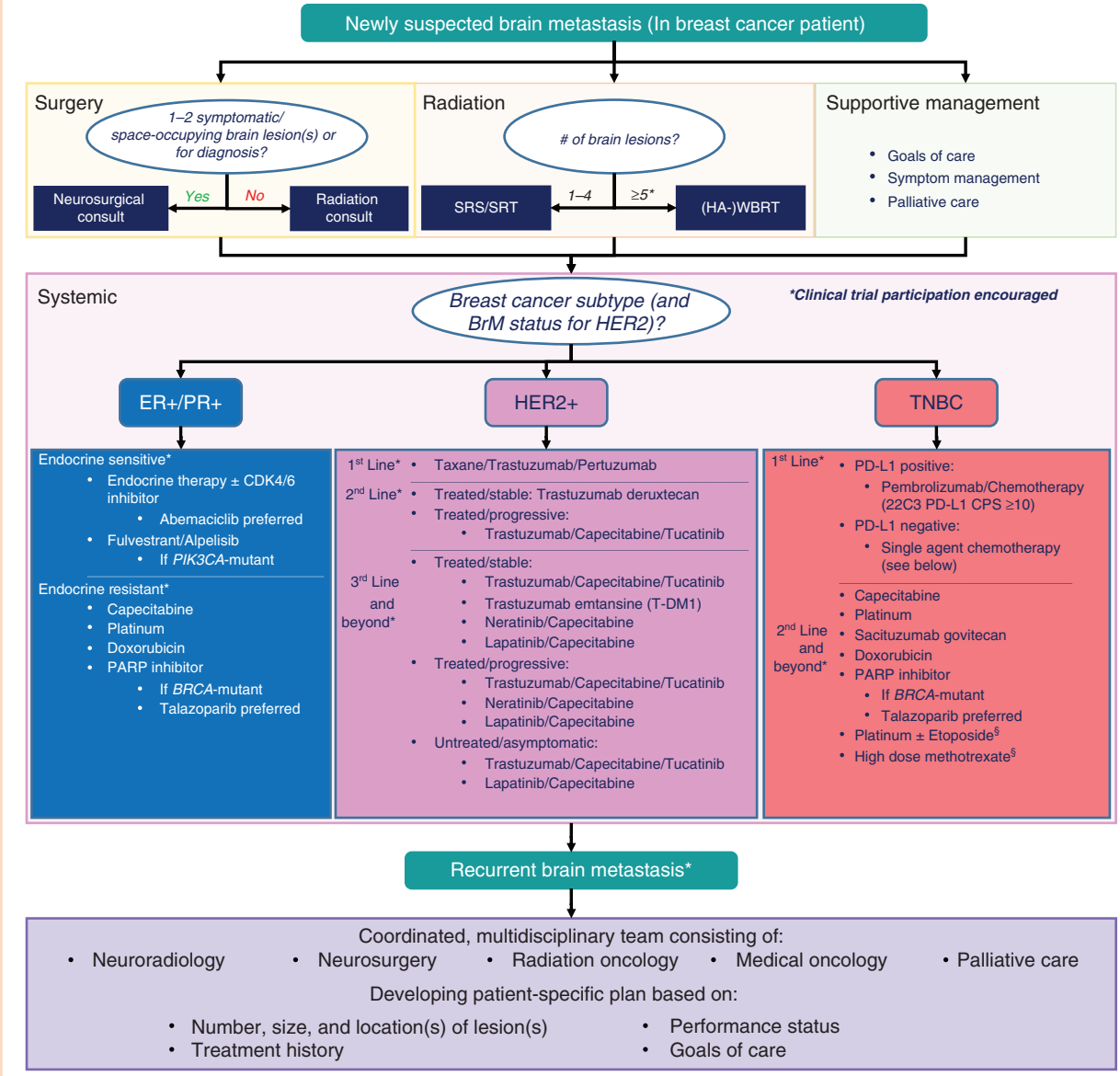


**Figure 1.** Treatment options for patients with newly suspected or recurrent breast cancer brain metastases, including surgery, radiation therapy, and systemic treatments. Strategies are based on level 1 evidence and NCCN guidelines. Randomized controlled trials to investigate stereotactic radiation approaches for 5–15 brain lesions are ongoing. Clinical trial participation is encouraged when appropriate. BrM, brain metastasis; ER+, estrogen receptor-positive; HER2+, human epidermal growth factor receptor 2-positive; PR+, progesterone receptor-positive; SRS, stereotactic radiosurgery; SRT, stereotactic radiotherapy; T-DM1, trastuzumab emtansine; TNBC, triple-negative breast cancer; (HA-)WBRT, (hippocampal avoidance) whole-brain radiotherapy. Recommendation per NCCN guidelines. *Clinical trial participation is encouraged.

For the patients with BCBrM, there was a 52% reduction in disease progression or risk of death (HR = 0.48, 95% CI: 0.34, 0.69; $P < .00001$).[3] The FDA approved tucatinib in combination with trastuzumab and capecitabine in April 2020 as a treatment for patients with HER2+ metastatic BC, including patients with BrM who have received one or more prior anti-HER2-based regimens in the metastatic setting. Based on the FDA-approved indication, tucatinib with capecitabine and trastuzumab could be considered in the second- or third line for patients with locally treated, yet progressive, BCBrM (Figure 1).

Neratinib with capecitabine has also shown intracranial efficacy in the treatment of HER2+ BCBrM. In a phase II, single-arm study of patients with measurable, progressive, HER2+ BCBrM (92% after receiving CNS surgery and/or radiotherapy), neratinib/capecitabine had a CNS ORR of 49% in lapatinib-naive (95% CI, 32%–66%) and 33% in lapatinib-treated (95% CI, 10%–65%) patients.[47] NALA (clinicaltrials.gov, Identifier: NCT01808573) was a phase III international, randomized, clinical trial of neratinib plus capecitabine vs lapatinib plus capecitabine in patients with HER2+ metastatic BC who had received ≥2 prior

**Table 4.** HER2-Targeting Agents for Breast Cancer Brain Metastases

| Agent | Class | Target(s) | iORR in BCBrM | PFS and/or OS in BCBrM |
|---|---|---|---|---|
| Trastuzumab (Herceptin) | mAb | HER2 | 11% (high-dose trast with pertuzumab)[39] | OS: 26.3 mos (with taxane)[38] |
| Pertuzumab (Perjeta) | mAb | HER2 | 11% (high-dose trast with pertuzumab)[39] | OS: 34.4 mos (with taxane/trast)[38] |
| (Ado-)Trastuzumab emtansine (T-DM1, Kadcyla) | ADC | HER2, microtubules | 49.3% (untreated[b])[42] | PFS: 5.5 mos[42]; 5.9 mos vs 5.7 mos (cape/lap)[41]<br>OS: 18.9 mos[42]; 26.8 mos vs 12.9 mos (cape/lap)[41] |
| (Fam-)Trastuzumab deruxtecan (DS-8201, T-DXd) | ADC | HER2, topo I | Unknown | PFS: 18.1 mos[44] |
| Lapatinib (Tykerb) | TKI (rev) | HER1/EGFR, HER2, HER4 | 65.9% (untreated)[45]<br>38% (treated progressive BrM with cape/lap)[46] | PFS: 5.5 mos[45]<br>OS: 17.0 mos[45] |
| Tucatinib (Tukysa)[a] | TKI (rev) | HER2, HER3 | 47.3% (untreated or treated progressive) vs 20.0% (placebo/cape/trast, untreated or treated progressive)[3] | CNS PFS: 9.9 mos (with cape/trast) vs 4.2 mos (placebo/cape/trast)[3]<br>OS: 18.1 mos vs 12 mos (placebo/cape/trast)[3] |
| Neratinib (Nerlynx) | TKI (irrev) | HER1/EGFR, HER2, HER4 | 49% (lap-naïve), 33% (lap-treated) (treated progressive with cape/neratinib)[47] | PFS: 5.5 mos (lap-naïve); 3.1 mos (lap-exposed)[47]<br>OS: 13.3 (lap-naïve) mos; 15.1 mos (lap-exposed)[47] |

ADC, antibody–drug conjugate; BCBrM, breast cancer brain metastases; cape, capecitabine; CNS, central nervous system; CSF, cerebrospinal fluid; HER, human epidermal growth factor receptor; lap, lapatinib; mos, months; OS, overall survival; PFS, progression-free survival; iORR, intracranial response rate; irrev, irreversible; mAb, monoclonal antibody; rev, reversible; TKI, tyrosine kinase inhibitor; see review[48]; topo, topoisomerase; trast, trastuzumab.

[a]FDA approved for BCBrM.

[b]≥30% reduction in sum of major diameters of previously untreated BCBrM.

HER2-directed regimens.[50] Time to intervention for symptomatic CNS disease (overall cumulative incidence 22.8% vs 29.2%; $P = .043$) was delayed with neratinib vs lapatinib. Efficacy of neratinib combinations following the use of tucatinib combinations is unknown. Other regimens recommended in the NCCN guidelines[51] specifically for the treatment of HER2+ BCBrM include capecitabine/lapatinib or paclitaxel/neratinib, though the efficacy of these agents after prior tucatinib-based regimens, pertuzumab, T-DM1, and trastuzumab deruxtecan remains unknown.

## Triple-Negative BCBrM

Historically, the mainstay of systemic therapy for TNBC BrM has been traditional chemotherapy. Based on NCCN guidelines,[51] options for chemotherapy in the setting of HER2- BCBrM include platinum therapy with or without etoposide or high-dose methotrexate.[51] Extrapolating from the HER2+ space and based on pharmacokinetic studies illustrating intracranial tumor accumulation of its metabolites, the oral 5-FU prodrug capecitabine is also an option.[52]

Several studies have illustrated deficient DNA damage repair in BCBrM compared to primary tumors.[53,54] Coupled with activity in *BRCA*-associated and/or altered TNBC and the brain permeability of several inhibitors of poly(ADP-ribose) polymerase (PARP), these inhibitors are also emerging as promising systemic therapy for BrM arising from TNBC.[55] A subset analysis of patients with *BRCA*-associated BrM enrolled to the EMBRACA study to either the PARP inhibitor, talazoparib vs physician's choice chemotherapy, illustrated improved PFS for those who received the PARP inhibitor (5.7 vs 1.6 months, HR 0.32, 95% CI: 0.15–0.68, $P = .0016$).[56] Case reports in patients with *BRCA*-mutated BrM support the activity of PARP inhibitors in the CNS and their use in these patients.[57–59]

Topoisomerase inhibitors are less frequently considered in advanced BC, when compared to other solid tumor types, including primary brain tumors.[60] Given the DNA damaging mechanism of action and brain permeability of the topoisomerase inhibitor, irinotecan, this chemotherapeutic was evaluated in a phase II study of patients with progressive TNBC BrM in combination with the anti-cancer agent iniparib (previously thought to be a PARP inhibitor).[61] While the response rate was low (4/34, 12%), 2 of the intracranial partial responses were seen in patients known to harbor a germline *BRCA* mutation. Time to progression and OS were reported at 2.14 months and 7.8 months, respectively.

Sacituzumab govitecan is a newer generation ADC targeting TROP-2 (trophoblast cell surface antigen-2) with a potent topoisomerase inhibitor SN-38 payload.

Results of the phase III ASCENT study for patients with advanced TNBC illustrated substantial improvement in PFS (5.6 vs 1.7 months, HR 0.41, $P < .0001$) and OS (12.1 vs 6.7 months, HR 0.48, $P < .0001$) compared to physician's choice of chemotherapy, respectively.[62] In a subgroup analysis of enrolled patients with BrM, PFS numerically favored sacituzumab (2.8 vs 1.6, HR 0.65, 95% CI: 0.35–1.22); there was no difference in OS (6.8 vs 7. 5 months, HR 0.87, 95% CI: 0.47–1.63).[63] Interestingly, in a window of opportunity study, intracranial tumor concentrations of sacituzumab and its metabolites were measured at 150-fold of the projected $IC_{50}$ among 4 patients with BCBrM treated with sacituzumab prior to standard-of-care craniotomy.[64] Sacituzumab govitecan is currently under investigation in HER2- treated but progressive BCBrM (clinicaltrials.gov, Identifier: NCT04647916).

The role of immunotherapy in the treatment of TNBC BrM is not yet clear. In the first-line treatment of metastatic TNBC, pembrolizumab is approved in combination with chemotherapy if tumors are deemed PD-L1-positive.[65] In the KEYNOTE-355 study of pembrolizumab with chemotherapy for first-line metastatic TNBC, only 3% of the patient population was enrolled with BrM, and individual outcomes for these patients are unknown.[66] Ongoing and planned clinical trials (Table 3) will help determine the impact of immunotherapy for TNBC BrM, including combination strategies with local therapies, either neurosurgical resection or focused radiation therapy.

## Discussion

Significant advances have been made over the past decade, both in local and systemic therapy approaches, for patients with BCBrM with corresponding improvements in outcomes. Local therapy techniques are becoming more focused and precise, yielding improved oncologic outcomes in a manner that preserves neurocognition and quality of life. Perhaps one of the greatest achievements has been the first FDA approval for a systemic therapy for patients with advanced HER2+ BCBrM. The inclusion of patients with BCBrM in clinical trials, including randomized, phase III studies, is increasing. Multidisciplinary management of patients with BCBrM remains critical to ensure adequate sequencing of local and systemic therapies to maximize survival and quality of life. Care of patients with recurrent BCBrM, in particular, requires a coordinated effort from a team of multidisciplinary providers to develop a personalized treatment plan based on each patient's case, considering factors such as the number and locations of BrM, the patient's treatment history, their disease status both intracranially and extracranially, and the patient's overall goals of care. Incorporation of symptom management and palliative care into the care team, and early on, is encouraged to address advanced care planning and patients' goals during their treatment trajectory. Continued innovations and coordinated care from our multidisciplinary teams, including our basic and translational scientists, will continue to move the field forward for our many patients with BCBrM.

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