Evolving treatment strategies of brain metastases from breast cancer: current status and future direction

Jae Sik Kim and In Ah Kim

Abstract: Remarkable progress in breast cancer treatment has improved patient survival, resulting in an increased incidence of brain metastasis (BM). Current treatment options for BM are limited and are generally used for palliative purposes. Historically, local treatment, consisting of radiotherapy and surgery, is the standard of care due to delivery limitations of systemic treatments through the blood–brain barrier. However, as novel biological mechanisms for tumors and BM have been discovered, several innovative systemic agents, such as small–molecular-targeted therapy and immunotherapy, have begun to change the treatment paradigm. In addition, efforts to maximize antitumor effects have been attempted using combination therapy, informed by tumor biology. In this comprehensive review, we will highlight various clinical trials investigating the treatment of BM in breast cancer patients, discuss presently available treatment options, and suggest potential directions of future therapeutic targets.

Keywords: brain metastasis, breast cancer, clinical trial, local treatment, systemic treatment

Introduction

Breast cancer (BC) is the second most common cancer which metastasizes to the brain.1 Among patients with metastatic BC, up to 30% eventually develop brain metastasis (BM).2 The incidence of BM is associated with molecular subtypes of BC and is likely to be higher with earlier occurrence in patients with human epidermal growth factor receptor 2 (HER2)-positive and triple-negative (TN) BC.3–7 In patients with metastatic HER2-positive and TNBC, the incidence of BM is 11–48% and 25–46%, respectively, while in patients with luminal A and B, incidences are 8–15% and 11%, respectively.7–13 Patients with BM experience neurologic dysfunction14 and have worse prognoses by molecular subtypes.15,16 The reported median overall survival (OS) for patients with luminal and HER2-positive disease was 7.1–18.9 and 13.1–16.5 months, respectively, while for patients with TNBC, OS was 4.4–4.9 months.6,17 Therefore, management of patients with BM from BC is a significant issue directly related to quality of life and survival. Moreover, the tumor subtypes should be considered when treating BM as well as when designing new clinical trials.

BC treatment has dramatically improved during recent decades, and effective treatment of extracranial disease has prolonged survival.18 Based on the report by Sperduto et al. that the median interval from primary BC to BM in HER2-positive patients was 35.8 months,4 the risk of developing BM would be increased as patients survive longer. Furthermore, intracranial spread is insufficiently controlled, also resulting in increased incidence of BM.8,19,20 After the introduction of trastuzumab, accelerated incidence of BM in HER2-positive patients has become common.21,22 Although surgical resection followed by radiotherapy could be curative for a small, solitary BM,23 current treatment options for large or multiple BM remain mainly palliative. Therefore, effective treatments for BM continue to be an unmet medical need.

Historically, patients with BM were treated with whole-brain radiotherapy (WBRT) or surgical
resection. However, due to concerns regarding WBRT-induced neurocognitive decline, stereotactic radiosurgery (SRS) is an alternative for limited BM. In addition, following the emergence of innovative targeted therapies and immunotherapies, the paradigm of BM treatment is beginning to shift from local to systemic treatment. Clinical trials investigating combinations of these are also increasing.

In this article, we summarize current local treatments for BM and review clinical trials of systemic therapies, mainly focusing on BM in HER2-positive and TNBC. We then highlight different systemic therapies that have been used in combination with radiotherapy (RT). Our discussion of ongoing clinical trials may encourage the development of new management strategies for BM.

**General local treatment for BM**

Currently, local treatment options for BM consist of surgery, SRS, WBRT, or combinations of these, regardless of the primary solid tumor. Many factors are considered during treatment selection, including patient preference, other comorbidities, and the number and volume of BMs. However, BM is classified into limited or extensive disease according to the number and volume of lesions, and treatment strategies are selected based on this classification. The definition of limited BM in National Comprehensive Cancer Network guideline is as follows: ‘Limited’ brain metastases defines a group of patients for whom SRS is equally effective and offers significant cognitive protection compared with WBRT. In general, one to four BMs are considered limited, and for these BMs, surgical resection and SRS are available local treatments. Patients with extensive BM or with symptomatic BM and uncontrolled extracranial disease could be candidates for WBRT, aimed at palliation; the median OS for patients receiving WBRT for BM from BC is approximately 4.2 months.

There is disagreement whether WBRT after complete surgical resection or SRS is necessary to eradicate microscopic disease at the primary BM or distant intracranial sites. Several randomized trials exploring this demonstrated that omission of WBRT resulted in significantly increased intracranial relapse (1-year local control rate was approximately 70% versus 90–100%) but did not affect OS except one trial (Table 1). Incidence of radionecrosis in those studies was 0.6–6.7% and 1.1–4.6% in the groups without and with adjuvant WBRT, respectively. Chang et al. reported the extremely high OS (63%) in the SRS-alone group, maybe due to more use of salvage therapies (87%) than other studies. Interestingly, in an individual patient data meta-analysis, younger patients (<50 years old) with SRS alone had significantly improved survival than those with SRS+WBRT (10 versus 8.2 months; p=0.04), with no difference in distant intracranial failure. The inferior survival of SRS+WBRT in this age group was thought to be due to side effects of WBRT, without a positive effect on distant brain relapse rates. In addition, although Aoyama et al. reported no difference in neurocognitive testing after treatment between groups, WBRT in patients with limited BM is not used due to the high risk of neurocognitive decline. Therefore, treatment guidelines recommend that SRS alone is preferred in patients with limited BM, while WBRT should be reserved for salvage.

An ongoing phase II study [ClinicalTrials.gov identifier: NCT02898727] is assessing the salvage WBRT rate within 1 year after surgical resection, SRS, or both, in HER2-positive patients with 1–5 BMs (Table 2). This study has two purposes: (a) investigate tumor control after surgery and/or SRS; and (b) evaluate BM development at new sites when WBRT is not given.

As mentioned previously, WBRT better controls intracranial disease, but is not widely used, especially in patients with limited disease, because of possible neurocognitive decline and lack of OS benefit. However, in one report, WBRT-induced tumor shrinkage resulted in better survival and preservation of neurocognitive function. Li et al. concluded that neurocognition was adversely correlated with BM progression, rather than WBRT. As an alternative approach, prospective studies of patients who underwent hippocampal-sparing WBRT revealed that functional preservation was achieved by reducing the bilateral hippocampi radiation dose. Furthermore, Gondi et al. presented results of a phase III trial (NRG CC01), demonstrating that hippocampal-sparing WBRT plus memantine better preserved neurocognitive function than non-hippocampal sparing, with similar intracranial control and survival. Several retrospective studies have reported improved survival after up-front WBRT in certain patient groups, including those with late-onset BM from a primary BC or a BC-specific graded prognostic assessment score of 0–2.
SRS delivers a single fraction of high radiation dose characterized by a very rapid dose fall-off around the BM. This confers the advantage of sparing normal brain tissues and expands the role of SRS in patients with limited BM, replacing WBRT. Even, SRS has frequently been used in patients with BMs beyond four in real practices, and some case series show a wide range of local control rates. Recently, a large multi-institutional retrospective study of 2089 patients analyzed treatment outcomes of initial SRS for BM. The median OS for patients with 2–4 BMs \((n = 882, 42\%)\) and 5–15 BMs \((n = 212, 10\%)\) was 9.5 and 7.5 months, respectively, showing no significant difference. The 1-year distant brain failure was 41\% for 2–4 BMs and 50\% for 5–15 BMs, respectively. JLGK0901 was a prospective observational study that enrolled 1194 patients with 1–10 BMs receiving SRS alone. Patients with 5–10 BMs had a similar OS as those with 2–4 BMs; there was no difference in acute toxicities. However, interpretation of these findings should be taken cautiously, as these studies were not randomized controlled studies. Future prospective studies are therefore needed to set appropriate indications for SRS alone.

### Table 1. Prospective randomized clinical trials for the treatment of brain metastases in breast cancer.

| Category | Author                  | Population characteristics | Phase | Treatment                                                                 | Overall survival | Other primary endpoints                                                                 |
|----------|-------------------------|----------------------------|-------|---------------------------------------------------------------------------|------------------|----------------------------------------------------------------------------------------|
| RT       | Aoyama et al.\(^{30}\) | 1–4 BMs \(\leq 3\) cm\(^*\) | III   | SRS alone \((n = 67)\) \(\text{versus SRS+WBRT (n = 65)}\) | 1 year: 28.4\% \(\text{versus 38.5\% (p = 0.42)}\) | HVL-R total recall at 4 months \(\text{(mean posterior probability of decline): 24\% versus 52\%} [p(A > B)** = 96\%]\) |
| RT       | Chang et al.\(^{24}\)   | 1–3 BMs \(\leq 4\) cm\(^*\) | III   | SRS alone \((n = 30)\) \(\text{versus SRS+WBRT (n = 28)}\)   | 1 year: 63\% \(\text{versus 21\% (p = 0.003)}\) |                                                                                          |
| RT       | Kocher et al.\(^{31}\)  | 1–3 BMs\(^*\)               | III   | OP or SRS \((n = 179)\) \(\text{versus OP or SRS+WBRT (n = 180)}\) | 2 years: 22.3\% \(\text{versus 22.6\% (p = 0.89)}\) | Median time to WHO PS deterioration \(> 2\): 10.0 months versus 9.5 months \(p = 0.71\) |
| RT       | Brown et al.\(^{32}\)   | 1–3 BMs \(\leq 3\) cm\(^*\) | III   | SRS alone \((n = 111)\) \(\text{versus SRS+WBRT (n = 102)}\) | Median: 10.4 months \(\text{versus 7.4 months (p = 0.92)}\) | Cognitive deterioration at 3 months: 63.5\% versus 91.7\% \(p < 0.001\) |
| TT+CT    | Lin et al.\(^{36}\)     | HER2-positive PD after RT/ trastuzumab | II    | Lapatinib+capecitabine \((n = 13)\) \(\text{versus lapatinib+topotecan (n = 9)}\) | CNS ORR\(^{\dagger}\): 38\% versus 0\% |                                                                                          |
| TT+CT    | Cortés et al.\(^{37}\)  | HER2-positive PD after trastuzumab \(+\) lapatinib | II    | Afatinib alone \((n = 40)\) \(\text{versus afatinib+vinorelbine (n = 38) versus TPC (n = 43)}\) | Clinical benefit rate\(^{\dagger}\) at 12 weeks: 30.0\% versus 34.2\% versus 41.9\% \(p = 0.37; p = 0.63\) |

\(^{*}\)Primary tumors were not confined to breast cancer.

\(^{**}\)Bayesian probability of a higher neurocognitive decline in SRS+WBRT than SRS alone.

\(^{1}\)Defined as a \(\geq 50\%\) volumetric reduction.

\(^{2}\)Defined as follows: \[a\] no progression of CNS per RECIST 1.1; \[b\] no worsening of tumor-related neurological signs or symptoms; \[c\] no corticosteroid dose increase; and \[d\] absence of extra-CNS disease progression.

\(^{3}\)Afatinib alone versus TPC, \(p = 0.37; \text{afatinib+vinorelbine versus TPC, p = 0.63.}\)

BM, brain metastasis; CNS, central nervous system; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; HVL-R, Hopkins Verbal Learning Test, Revised; OP, operation; ORR, objective response rate; PD, progressive disease; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; SRS, stereotactic radiosurgery; TPC, treatment of physician’s choice; TT, targeted therapy; WBRT, whole-brain radiotherapy; WHO PS, World Health Organization performance status.
Table 2. Ongoing clinical trials associated with radiotherapy for the treatment of brain metastases in breast cancer.

| Category | Treatment | Population characteristics | Phase | ClinicalTrials.gov NCT identifier | Status* (study start date) | Primary endpoint |
|----------|-----------|-----------------------------|-------|----------------------------------|---------------------------|------------------|
| OP/RT    | HER2-positive 1-5 BMs          | II   | Recruiting [November 2017] | OP with or without SRS boost SRS only (20Gy/1x-24Gy/3x) | OP/RT HER2-positive 1-5 BMs | Ongoing, Salvage WBRT rate |
|          | HER2-positive 1-10 BMs (<3 cm) | II   | Recruiting [July 2019]     | FSRT (8Gy × 3-5 fx) | FSRT HER2-positive 1-10 BMs (<3 cm) | Ongoing, Intracranial tumor control rate |
| RT       | All molecular subtypes WBR not suitable for OP or SRS | II   | Recruiting [July 2019]     | BEP followed by WBRT WBRT alone | BEP followed by WBRT WBRT-alone | Ongoing, Complete response rate per RECIST 1.1 |
| TT+RT    | TNBC <5 BMs                  | I/II | Recruiting [May 2018]     | Pembrolizumab+SRS Pembrolizumab+SRS alone | Pembrolizumab+SRS Pembrolizumab+SRS Alone | Ongoing, Brain-specific PFS |
| IT+RT    | All molecular subtypes 2-10 BMs (<4 cm) | I    | Recruiting [November 2018] | Nivolumab+SRS Nivolumab+SRS | Nivolumab+SRS Nivolumab+SRS | Ongoing, Dose-limiting toxicity |
| TT+RT    | HER2-positive ≥2 BMs          | I    | Recruiting [January 2019]  | T-DM1, concomitant with WBRT T-DM1, during WBRT | T-DM1, concomitant with WBRT T-DM1, during WBRT | Ongoing, Optimal sequence** |

*From http://clinicaltrials.gov, last accessed April 2020.

**Determined by acute toxicities and T-DM1 pharmacokinetics of blood/cerebrospinal fluid.

BM, brain metastasis; CT, chemotheraphy; FFRT, fractionated stereotactic radiotherapy; fX, fractions; HER2, human epidermal growth factor receptor 2; IT, immunotherapy; NCI, National Cancer Institute; OS, overall survival; PSFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumors; RT, radiotherapy; SRS, stereotactic radiosurgery; T-DM1, ado-trastuzumab emtansine; TNBC, triple-negative breast cancer; WBRT, whole-brain radiotherapy.
Fractionated stereotactic radiotherapy (FSRT) introduces the radiobiological advantages of fractionation to SRS, including lower toxicity to normal tissues, and is an option for treatment of large BMs or those close to critical normal tissues and not amenable for SRS. A systematic review of 10 retrospective or prospective studies, concluded that FSRT provided a local control rate of 80% at 1 year and 69% at 2 years.\(^4^6\) The rate of radionecrosis after FSRT for large BMs (median 1.7–4.4 cm in diameter or 2.04–17.5 cm\(^3\)) was 0–9%.\(^4^7\) Considering the large volumes that were irradiated, these toxicity rates might be acceptable. A phase II study [ClinicalTrials.gov identifier: NCT04061408] is enrolling HER2-positive patients with 1–10 BMs, predicting better local control and lower radionecrosis after FSRT (Table 2).

In summary, there are currently no strict guidelines for local treatment strategies for patients with BM. Physicians should carefully weigh the benefits of local treatment based on individual patient and disease characteristics. Further studies are needed to select patients who will benefit from local treatments and to overcome the limitations of current options.

### Advancement of systemic treatments for BM in BC

The brain is shielded from the body’s bloodstream by a physical barrier, the blood–brain barrier (BBB), which is formed by endothelial cells and their tight junctions, a thick basement membrane of pericytes, and astrocytic end-foot processes.\(^4^8\) It acts as a selective filter, limiting the penetration of most cytotoxic agents, resulting in low efficacy of systemic agents. In fact, only a few drugs could penetrate the BBB.\(^4^8,4^9\) As BM develops, the BBB integrity weakens and lipophilic drugs could pass through the BBB more easily, but the efflux pumps of the BBB bring them out again.\(^5^0\)

Generally, because of the limitations of crossing the BBB, as well as the poor prognosis of BM and potential central nervous system (CNS) toxicities, many clinical trials investigating systemic treatments for metastatic BC have excluded patients with BM.\(^5^1\) However, development of systemic treatments has improved the control of extracranial disease, and as survival increases, the necessity of clinical trials in patients with BM is emerging. Various approaches to enhance drug delivery through the BBB have been attempted, including: (a) designing new drugs with low molecular weight; (b) modifying existing agents; (c) implementing intermittent high-dose drug regimens with alternative schedules; and (d) disrupting the BBB using chemical or mechanical means.\(^5^2\)

In the following sections, we will discuss the advancement of systemic treatment options for BM in BC, especially in HER2-positive or TNBC. Table 1 lists prospective randomized studies enrolling only patients with BM, and Tables 2 and 3 list systemic therapies currently being developed, with the hope they will provide new insights for BM management.

#### Era of new HER2-targeted therapy

Trastuzumab, the first anti-HER2 antibody, is effective at controlling extracranial disease in HER2-positive patients, and has dramatically improved survival.\(^5^3\) However, due to its large molecular weight (~148 kDa), its delivery across the BBB is limited.\(^5^4\) For this reason, new HER2-directed therapies are currently being developed.

Pertuzumab, a recombinant humanized monoclonal antibody (~148 kDa), binds to a different HER2 site than trastuzumab, preventing HER2/HER3 dimerization and providing complementary action when combined with trastuzumab.\(^5^5\) The CLEOPATRA trial randomized metastatic HER2-positive patients with no prior chemotherapy or HER2-directed therapy into pertuzumab (or placebo) + trastuzumab + docetaxel groups.\(^5^6\) Long-term follow up (median 50 months) revealed that the pertuzumab combination significantly improved OS with an absolute difference of 15.7 months [median (95% confidence interval (CI)), 56.5 months (49.3–not reached)]\(^5^7\) versus 40.8 (35.8–48.3)]. Thus, pertuzumab in combination with trastuzumab and docetaxel became standard first-line therapy in this population. Despite the exclusion of patients with CNS metastases and almost similar incidence of CNS metastases in this trial, the onset of CNS metastases was delayed in the pertuzumab combination group compared with the placebo group [median 15.0 \textit{versus} 11.9 months, hazard ratio (HR) 0.58, 95% CI 0.39–0.85, \(p = 0.005\)].\(^5^7\) This result shows the potential role of pertuzumab in the treatment of BM. PATRICIA [ClinicalTrials.gov identifier: NCT02536339] is a phase II study assessing the safety and efficacy of pertuzumab.
HER2-targeted tyrosine kinase inhibitors (TKIs) that penetrate the BBB are used in clinical practice and are being investigated in clinical trials, including: lapatinib,\textsuperscript{36,59–63} neratinib,\textsuperscript{64–67} afatinib,\textsuperscript{37,68} tucatinib,\textsuperscript{69–73} pyrotinib,\textsuperscript{74,75} and epertinib.\textsuperscript{76} Lapatinib is an orally bioavailable and small dual TKI that binds HER2 and the epidermal growth factor receptor.\textsuperscript{59} A phase II study of lapatinib as a single agent in pretreated patients was disappointing, with a volumetric CNS ORR of 6%.\textsuperscript{60} However, when combined with capecitabine in a randomized phase II study, the response rate increased to 38% (Table 1).\textsuperscript{36} LANDSCAPE, a phase II study, evaluated lapatinib+capecitabine for HER2-positive patients with previously untreated BM.\textsuperscript{61} Surprisingly, CNS ORR (volumetric) was 65.9% (95% CI 50.1–79.5), suggesting that instead of cranial RT, up-front lapatinib+capecitabine is a feasible first-line treatment for BM in HER2-positive BC. However, this high CNS ORR should be interpreted considering that patients did not receive current, standard, first-line treatment for BM, and needs to be demonstrated in randomized control trials. Recently, a phase I study of 11 patients with CNS metastases illustrated that intermittent high-dose lapatinib (1500 mg bid) is tolerable when alternated with capecitabine.\textsuperscript{62} The LAPTEM phase I trial assessed lapatinib+temozolomide and showed favorable safety and efficacy.\textsuperscript{63} These novel strategies warrant further investigation.

Neratinib is an oral, irreversible TKI of the pan-HER family.\textsuperscript{64} The Translational Breast Cancer Research Consortium (TBCRC) 022 initiated a phase II trial to investigate the efficacy of neratinib for patients with pretreated, progressive BM in HER2-positive BC. This trial consists of three cohorts: Cohort 1, neratinib monotherapy; Cohort 2, neratinib with surgical resection; and Cohort 3, neratinib+capecitabine without (3a) and with (3b) previous lapatinib treatment. In Cohort 1, 40 patients were enrolled, and 78% of patients had a history of receiving WBRT.\textsuperscript{65} Only three patients showed a partial response in CNS lesions according to composite criteria (ORR 8%). The composite CNS ORR in Cohort 3a and 3b were 49% (95% CI 32–66) and 33% (95% CI 10–65), respectively.\textsuperscript{66} Median progression-free survival (PFS) and OS were 5.5 and 13.3 months in Cohort 3a, respectively, and were 3.1 and 15.1 months in Cohort 3b, respectively. The most common grade ≥3 toxicity was diarrhea in Cohort 1 (25%) and Cohort 3a/b (29%).\textsuperscript{65,66} TBCRC 022 also designed a Cohort 4 [ClinicalTrials.gov identifier: NCT01494662] to evaluate neratinib and ado-trastuzumab emtansine (T-DM1; Table 3). The results of NALA, a randomized phase III trial, were presented in 2019.\textsuperscript{67} Neratinib+capecitabine was compared with lapatinib+capecitabine in metastatic HER2-positive patients, as a third- or later-line HER2-directed therapy. PFS improved (HR 0.76; \( p = 0.006 \)), and OS tended to be longer (HR 0.88; \( p = 0.209 \)) in the neratinib combination group. This trial excluded active BM, but asymptomatic CNS metastases were included. Neratinib+capecitabine postponed time to intervention for symptomatic CNS (overall cumulative incidence, 22.8% \textit{versus} 29.2%; \( p = 0.043 \)). However, grade 3 diarrhea in these patients was more frequent than in lapatinib+capecitabine-treated patients (24.4% \textit{versus} 12.5%).

Afatinib is an oral, irreversible HER1 and HER2 TKI.\textsuperscript{68} A total of 121 patients with progressive/recurrent BM while receiving HER2-targeted therapies (trastuzumab, lapatinib, or both) were randomized into afatinib alone, afatinib+vinorelbine, or treatment of physician’s choice (TPC) in a phase II study (Table 1).\textsuperscript{37} The primary endpoint was clinical benefit 12 weeks after randomization and was assessed as follows: (a) no progression of CNS per Response Evaluation Criteria In Solid Tumors (RECIST) 1.1; (b) no worsening of tumor-related neurological signs or symptoms; (c) no corticosteroid dose increase; and (d) absence of extra-CNS disease progression. Unexpectedly, clinical benefit was mostly achieved in the TPC group (41.9%), though was not statistically significant. In addition, toxicity profiles were worse in afatinib-containing treatments. These disappointing results have almost put an end to further afatinib research. A randomized phase II trial [ClinicalTrials.gov identifier: NCT04158947] is preparing, which will investigate the combination of another HER2-targeted agent, T-DM1, with afatinib (Table 3).

Another promising agent is tucatinib, an orally administered, selective, and reversible HER2 TKI, which reduces diarrhea and rash compared...
| Category | Population characteristics | Phase | Treatment | Primary endpoint | ClinicalTrials.gov NCT identifier | Status* (study start date) |
|----------|-----------------------------|-------|-----------|------------------|----------------------------------|---------------------------|
| TT+TT    | HER2-positive PD/recurrent BM after RT | II    | Pertuzumab + high-dose trastuzumab | CNS ORR by RANO-BM | NCT02536339 | Active, not recruiting (December 2015) |
| TT+TT    | HER2-positive Cohort 4a: untreated BM Cohort 4b: PD of BM without prior T-DM1 Cohort 4c: PD of BM with prior T-DM1 | II    | Neratinib + T-DM1 | CNS ORR by composite criteria | NCT01494662 | Recruiting (February 2012) |
| TT+TT    | HER2-positive PD/recurrent BM after HER2-directed therapy** | I/II (randomized) | Afatinib + T-DM1 T-DM1 alone | (a) Safety and tolerability of T-DM1 and Afatinib (b) CNS ORR | NCT04158947 | Not yet recruiting (January 2020) |
| TT+TT    | HER2-positive | I (randomized) | Tucatinib (b.i.d.) + trastuzumab Tucatinib (q.d.) + trastuzumab | Maximum tolerated dose | NCT01921335 | Active, not recruiting (August 2013) |
| TT+CT    | HER2-positive | II    | Pyrotinib + capecitabine | CNS ORR | NCT03691051 | Not yet recruiting (November 2018) |
| TT+CT    | HER2-positive Previous CT (anthracycline and taxane) | II    | Pyrotinib + vinorelbine | CNS ORR by RANO-BM | NCT03939892 | Recruiting (December 2018) |
| TT+CT    | All molecular subtypes Including LMS Recurrent/PD after WBRT | II    | BEEP (+ ITM in patients with LMS) | CNS ORR by volumetric criteria | NCT01281696 | Completed in October 2013 |
| TT+CT    | All molecular subtypes Previous WBRT or SRS | II    | BKM 120 + capecitabine (+ trastuzumab for HER2-positive) | Clinical benefit rate‡ | NCT02000882 | Completed in March 2019 |

(Continued)
| Category | Population characteristics | Phase | Treatment | Primary endpoint | ClinicalTrials.gov NCT identifier | Status* (study start date) |
|----------|---------------------------|-------|-----------|------------------|-----------------------------------|---------------------------|
| TT+TT (+OP) | HER2-positive | II | Cohort A: GDC-0084+trastuzumab Cohort B: GDC-0084+trastuzumab+OP | CNS ORR by RANO-BM | NCT03765983 | Recruiting (February 2019) |
| CT | All molecular subtypes | II | ANG1005 (trastuzumab for HER2-positive) | CNS ORR | NCT01480583 | Completed in October 2015 |
| CT | All molecular subtypes Previous CT (anthracycline, taxane, and capecitabine) III (randomized) | Etrinotecan pegol (NKTR-102) TPC§ | OS | NCT02915744 | Active, not recruiting (November 2016) |
| CT | All molecular subtypes | II | Eribulin mesylate | CNS PFS at 12 weeks | NCT02581839 | Active, not recruiting (November 2015) |
| CT | All molecular subtypes Previous CT (anthracycline and taxane) PD after RT | II | Eribulin mesylate | CNS ORR by RANO-BM | NCT03412955 | Recruiting (March 2017) |
| CT+TT | HER2-positive Previous SRS, OP, or WBRT I/II (randomized) | Cohort 1, phase I: temozolomide+T-DM1 Cohort 2A, phase II: T-DM1 alone Cohort 2B, phase II: temozolomide+T-DM1 | (a) Maximum tolerated dose (b) Median time to progression | NCT03190967 | Recruiting (April 2018) |

*From http://clinicaltrials.gov, last accessed April 2020.
**Including trastuzumab and/or lapatinib, pyrotinib, and tucatinib.
†Defined as the best overall response rate of complete response, partial response, or stable disease in the CNS, reported as sustained for ≥24 weeks.
§One of the following seven agents: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel.
BEEP, bevacizumab, etoposide, and cisplatin; b.i.d., bis in die [twice daily]; BM, brain metastasis; CNS, central nervous system; CT, chemotherapy; HER2, human epidermal growth factor receptor 2; ITM, intrathecal methotrexate; LMS, leptomeningeal seeding; NCT, National Clinical Trial; OP, operation; ORR, objective response rate; OS, overall survival; PD, progressive disease; PFS, progression-free survival; q.d., quaque die [four times daily]; RANO-BM, Response Assessment in Neuro-Oncology Brain Metastases; RT, radiotherapy; SRS, stereotactic radiosurgery; T-DM1, ado-trastuzumab emtansine; TPC, treatment of physician’s choice; TT, targeted therapy; WBRT, whole-brain radiotherapy.
with other HER2 TKIs. Tucatinib with capecitabine and trastuzumab was tested in a phase I study for metastatic HER2-positive patients with or without treated stable BM. Twelve patients treated with 300 mg twice-daily tucatinib had measurable BM and five patients (42%) experienced brain-specific objective response by modified RECIST. A phase II randomized, double-blind study, HER2CLIMB, validated the treatment outcomes of this regimen and further included patients with BM which did not need immediate local intervention. The tucatinib combination prolonged PFS (HR 0.54, 95% CI 0.42–0.71; \( p < 0.001 \)) and OS (HR 0.66, 95% CI 0.50–0.88; \( p = 0.005 \)) compared with placebo. For patients with BM, the addition of tucatinib still improved PFS (HR 0.48, 95% CI 0.34–0.69; \( p < 0.001 \)). As other combination regimens, phase I studies of tucatinib combined with trastuzumab [ClinicalTrials.gov identifier: NCT01921335; Table 3] or T-DM1, even enrolling patients with progressive CNS lesions unless requiring immediate local therapy, reported CNS ORR as 8% and 36%, respectively. Now, a randomized, double-blinded, phase III study [ClinicalTrials.gov identifier: NCT03975647], also known as HER2CLIMB-02, is recruiting patients with advanced or metastatic HER2-positive BC. The criteria for enrollment of patients with BM are the same as in the previous phase I study. Patients will be randomly assigned to T-DM1 + tucatinib or placebo, and the primary endpoint is PFS. Tucatinib has received US Food and Drug Administration approval in combination with trastuzumab and capecitabine for women with previously treated advanced HER2+ breast cancer, with or without BM.

Pyrotinib is an oral, irreversible TKI targeting HER1, HER2, and HER4. In a randomized phase III study, pyrotinib was assessed against placebo, both administered with capecitabine, for patients with metastatic HER2-positive BC who had prior taxane and trastuzumab treatment. Pyrotinib + capecitabine achieved significantly longer PFS (median 11.1 versus 4.1 months; \( p < 0.001 \)); however, this trial did not enroll patients with untreated, symptomatic BM. Two phase II trials [ClinicalTrials.gov identifiers: NCT03691051, NCT03933982] have been initiated to investigate the antitumor activity of pyrotinib on BM (Table 3).

In January 2020, a phase I/II study of epertinib in refractory metastatic HER2-positive including BM BC reported that combination of epertinib with trastuzumab ± capecitabine had promising antitumor activity with favorable toxicity profiles. These results encourage more studies to investigate new HER2-directed combination therapies.

Other innovative molecular-targeted therapy
Based on the advances in the understanding of the underlying mechanisms of BC and BM, several molecular-targeted therapies have been developed in the last decade and have become some of the main therapeutic interventions for metastatic BC. Bevacizumab, a humanized vascular endothelial growth factor (VEGF) monoclonal antibody, is thought to transiently normalize peritumoral vessels, resulting in enhanced drug delivery to BM. The following three phase II trials attempted to demonstrate this hypothesis using a combination of bevacizumab and other cytotoxic agents. Thirty-eight patients with progressive BM were assigned to bevacizumab on day 1 of a 3-week cycle, followed by carboplatin and trastuzumab if HER2-positive on day 8 of one cycle and day 1 of subsequent cycles. Notably, this treatment schedule achieved a high CNS ORR according to the volumetric criteria of 77.1%, and 54.3% by RECIST. A third study [ClinicalTrials.gov identifier: NCT01281696] tested a similar regimen and included patients with leptomeningeal seeding, who would be treated with intrathecal methotrexate (Table 3). Pilot studies showed promising efficiency in leptomeningeal seeding patients. Additional investigation is needed to optimize the proper treatment period and chemotherapeutic agent combination.

Cabozantinib is a small, multiple TKI that inhibits MET and VEGF receptor-2, penetrates into the CNS, and has significant antitumor activity for BM in non-small cell lung cancer and renal-cell carcinoma. In patients with heavily pretreated BM in BC, cabozantinib was well tolerated but did not show sufficient CNS response [CNS ORR (per RECIST 1.1) 5.6%], in contrast with the previous studies showing higher CNS ORR after anti-VEGF. Therefore, further investigations...
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are needed to find out more detailed antitumor mechanisms underlying the VEGF pathway of BM from BC, which could explain the different antitumor activities of these two agents.

Another treatment strategy actively being investigated is inhibition of the phosphoinositide-3-kinase/mammalian target of rapamycin (PI3K/mTOR) pathway. Hyperactivation of this pathway is a mechanism of trastuzumab resistance. A phase II study, LCCC 1025, investigated whether inhibition of PI3K/mTOR and HER2 might lead to more significant responses in patients with HER2-positive BM. Everolimus, a small molecule of the mTOR complex 1 inhibitor, was given with trastuzumab and vinorelbine; the intracranial response rate was very low (4%) and only one patient experienced a partial response. However, a similar time to progression and OS as previous studies, and a clinical benefit rate of 65% at 6 months, indicated further research is needed. Several agents targeting PI3K, such as BKM120 [ClinicalTrials.gov identifier: NCT02000882] and GDC-0084 [ClinicalTrials.gov identifier: NCT03765983], are currently under investigation (Table 3). Other randomized trials are being pursued to validate this novel agent.

Cyclin-dependent kinase (CDK) 4/6 inhibitors have been developed, especially focusing on hormone receptor (HR)-positive/HER2-negative metastatic BC, and have significantly improved PFS in these populations. However, previous clinical trials of CDK4/6 inhibitors excluded patients with CNS metastasis or included patients with pretreated and stable BM, demonstrating limited evidence of their CNS efficacy. In a phase II study, abemaciclib, one of the CDK4/6 inhibitors, showed an intracranial clinical benefit of 25% among 58 patients with heavily pretreated BM from HR-positive/HER2-negative BC. In HER2-positive and TNBC, the use of CDK4/6 inhibitors (palbociclib, ribociclib, and abemaciclib, etc.) in metastatic settings with or without untreated BM, are currently under investigation. Disappointingly, a phase II study [ClinicalTrials.gov identifier: NCT02774681] of palbociclib in patients with HER2-positive BM was terminated due to slow accrual.

In TNBC, poly-adenosine diphosphate-ribose polymerase (PARP) inhibitors have been of interest. TBCRC 018 demonstrated that iniparib+irinotecan showed a slight benefit of time to progression in patients with progressive TNBC BM. However, iniparib is not currently considered a bona fide PARP inhibitor. Other PARP inhibitors, olaparib and veliparib, are currently not candidates for the treatment of BM. A case report demonstrated the potential role of olaparib in BM, while a phase II study [ClinicalTrials.gov identifier: NCT02595905], including BM patients, has been initiated to investigate cisplatin with or without veliparib.

**Return of classic chemotherapy**

One approach for facilitating penetration of chemotherapy agents through the BBB for BM treatment is to modify their structures through conjugation with a peptide vector or via pegylation. ANG1005 (GRN1005) makes Angiopep-2, a peptide vector that facilitates paclitaxel transport into the CNS. Importantly, ANG1005 showed no CNS toxicity in a phase I trial. In addition, a phase II study of ANG1005 in patients with recurrent BM showed excellent antitumor activity in intracranial and extracranial lesions. A phase II trial [ClinicalTrials.gov identifier: NCT01480583] testing ANG1005 (+ trastuzumab, if HER2 positive) was completed, but results are not available (Table 3). Other randomized trials are being pursued to validate this novel agent.

Etirinotecan pegol (NKTR-102), the prodrug of irinotecan, is a novel long-acting topoisomerase-I inhibitor, consisting of a four-arm polyethylene glycol with one irinotecan at the end of each arm. It slowly hydrolyzes *in vivo*, and continuously produces SN38, the active irinotecan metabolite, which prevents high plasma concentrations of irinotecan and SN38, as well as unwanted side effects. The phase III BEACON trial assessed the superiority of etirinotecan pegol to the currently available TPC in patients with locally recurrent or metastatic BC, who had prior treatment with an anthracycline, a taxane, and capecitabine. Patients were randomized to etirinotecan pegol or single-drug TPC (one of: eribulin, ixabepilone, vinorelbine, gemcitabine, paclitaxel, docetaxel, or nab-paclitaxel). This trial failed to show an OS improvement in the etirinotecan pegol arm, but in the subgroup analysis of OS, patients with BM had superior OS (median 10 versus 4.8 months) with an HR of 0.51 (95% CI 0.30–0.86). Although a small number of
patients with BM were included in this analysis, the survival benefit of etirinotecan pegol was clear with favorable safety. Based on these results, another phase III trial in this population with BM (ATTAIN) [ClinicalTrials.gov identifier: NCT02915744] is underway (Table 3).

Tesetaxel is of the taxane class of drugs, with an advantage of oral administration. In phase II study with locally advanced or metastatic HER2-negative and HR-positive BC patients, tesetaxel showed significant activity as a single agent, with an ORR per RECIST 1.1 of 45% (95% CI 29–62). Tesetaxel with or without capcitabine is being investigated in the randomized phase III study, CONTESSA [ClinicalTrials.gov identifier: NCT03326674], for these patients. CONTESSA TRIO [ClinicalTrials.gov identifier: NCT03952325] is a two-cohort, phase II study of tesetaxel. In Cohort 1, patients with locally advanced or metastatic TNBC will be randomized to tesetaxel or three inhibitors of programmed cell death-1 (PD-1) or its ligand (PD-L1; nivolumab, pembrolizumab, or atezolizumab). In Cohort 2, elderly patients (≥65 years old) with HER2-negative locally advanced or metastatic disease will receive tesetaxel mono-therapy. In this study, stable or progressing CNS metastases, excluding leptomeningeal disease are permitted but not required.

Establishing the efficacy of existing drugs against BM is as important as development of new agents. In a phase II trial, epothilone B did not achieve prespecified efficacy criteria, but increased diarrhea. In addition, a recent article suggested that irinotecan + temozolomide could be a treatment option for progressing CNS diseases. Eribulin mesylate, an approved agent for metastatic BC, is being tested in phase II trials [ClinicalTrials.gov identifier: NCT02581839 and NCT03412955; Table 3] for BM. A temozolomide and T-DM1 combination is being evaluated in a recruiting phase I/II study in patients with HER2-positive BM with prior local treatment [ClinicalTrials.gov identifier: NCT03190967; Table 3].

Prospects of immunotherapy
Over the past several years, the most revolutionary advancement in cancer treatment has been the discovery of immune-checkpoint inhibitors (ICIs). A mechanism of tumor survival and metastasis is activation of the immune-checkpoint pathway to induce immunosuppressive conditions. ICI blocks this activation, thereby increasing immunemediated tumor cell killing. After approval of ipilimumab, which targets cytotoxic T-lymphocyte antigen-4 (CTLA-4), for advanced melanoma treatment in 2011, several immunotherapeutic monoclonal antibodies have been developed to interrupt PD-(L)1 and CTLA-4 activity and have antitumor activity. The efficacy of immunotherapy in BM is well established in melanoma, non-small cell lung cancer, and renal-cell carcinoma (Table 4). Importantly, a review by Di Giacoma illustrated that intracranial ORR in melanoma was 5–26% with ICI monotherapy and 46–55% with ICI combination, suggesting that future studies should focus on the synergism of ICI-based therapeutic combinations (Table 4).

In metastatic TNBC, atezolizumab, a monoclonal antibody against PD-L1, in combination with nab-paclitaxel, was approved recently as first-line therapy based on the results of the IMpassion 130 trial. In this randomized phase III trial, 902 patients with untreated metastatic TNBC were assigned to receive atezolizumab or placebo, combined with nab-paclitaxel. Addition of atezolizumab to nab-paclitaxel significantly improved PFS compared with placebo (median 7.2 versus 5.5 months; HR 0.80, 95% CI 0.69–0.92; p=0.002). Median OS was longer in the atezolizumab + nab-paclitaxel group (21.3 months) than in the placebo + nab-paclitaxel group (17.6 months; p=0.08). Although subgroup analysis showed no PFS benefit in patients with BM, approximately only 7% of patients in each arm had BM, and combined chemotherapy was not optimal for CNS metastases. Future clinical trials of atezolizumab might be designed to evaluate clinically meaningful benefit in patients with BM from TNBC.

Another randomized phase III study, the KEYNOTE-355 trial [ClinicalTrials.gov identifier: NCT02819518], was released in a press in February 2020. This trial recruited patients with locally recurrent unresectable or metastatic TNBC, not previously treated with chemotherapy, and did not exclude patients with BM if they were treated and stable. This study consisted of two parts: in part one, pembrolizumab, an anti-PD-1, was administered with one of three chemotherapeutic agents chosen by investigators (nab-paclitaxel, paclitaxel, or gemcitabine/carboplatin); in part two, 847 patients were randomized to receive pembrolizumab or placebo, in combination with one of the three chemotherapy regimens. The interim analysis demonstrated that
| Immune-checkpoint inhibitor | Primary tumor | Population characteristics | Phase | Intracranial ORR | Overall survival |
|-----------------------------|---------------|----------------------------|-------|------------------|------------------|
| Atezolizumab                | NSCLC         | Asymptomatic supratentorial BM (n = 85) | III | Not reported | Median: 20.1 months |
|                             |               | Cohort A: asymptomatic BM (n = 51) | II | [mWHO, irORR] | Cohort A: 16%, Cohort B: 5% |
|                             |               | Cohort B: symptomatic BM (n = 21) | II | [mWHO, irORR] | Cohort A: 30%, Cohort B: 30% |
| Ipilimumab                  | Melanoma      | Cohort A: asymptomatic BM (n = 51) | II | (modified RECIST) | Cohort A: 16%, Cohort B: 16% |
|                             |               | Cohort B: symptomatic BM (n = 18) | II | (modified RECIST) | Cohort A: 55%, Cohort B: 17% |
| Ipilimumab + nivolumab      | Melanoma      | Cohort A: asymptomatic BM (n = 20) | II | [RECIST 1.1] | Cohort A: 30% |
|                             |               | Cohort B: untreated BM (n = 28) | II | [RECIST 1.1] | Cohort B: 29% |
| RCC                        | Melanoma      | Cohort A: asymptomatic, untreated BM (n = 35) | II | [modified RECIST] | Cohort A: 26% |
|                             |               | Cohort B: symptomatic BM or local therapy (n = 16) | II | [modified RECIST] | Cohort B: 26% |
|                            | RCC           | Asymptomatic, untreated BM (n = 28) | III/IV | [RECIST 1.1] | NA* |
| Nivolumab                   | RCC           | Treated stable BM (CheckMate 063 (n = 3), 017 (n = 9), and 057) | II | PR + SD: 33% | Median: 5.0 months |
|                            | RCC           | Asymptomatic BM, progressive after VEGFR-directed therapy (CheckMate 063 (n = 3), 017 (n = 9), and 057) | II | [RECIST 1.1] | Cohort A: 67%, Cohort B: 12% |
| Pembrolizumab               | Melanoma      | Asymptomatic, untreated BM (n = 23) | II | [modified RECIST] | Cohort 1: 30%, Cohort 2: 0% |
|                            | NSCLC         | Active BM (CheckMate 063 (n = 3), 017 (n = 9), and 057) | II | [RECIST 1.1] | Median: 17 months |
|                            |               | Cohort 1: PD-L1 positive (n = 3), Cohort 2: PD-L1 negative or unmeasurable (n = 5) | II | [modified RECIST] | Median: 1/2 years |

*Pooled analysis of the three prospective trials: CheckMate 063 (phase III), 017 (phase III), and 057 (phase III).

BM, brain metastasis; mWHO, modified World Health Organization criteria; NA, not applicable; NSCLC, non-small-cell lung cancer; ORR, overall response rate; PD-L1, programmed death-ligand 1; RECIST, Response Evaluation Criteria in Solid Tumors; SD, stable disease; VEGFR, vascular endothelial growth factor receptor.
pembrolizumab with chemotherapy significantly improved PFS compared with the placebo group (i.e. chemotherapy alone) in patients with a PD-L1 combined positive score of $\geq 10$ tumors. This trial continues to assess OS, the other primary endpoint.

Currently, other randomized phase III studies using pembrolizumab [ClinicalTrials.gov identifier: NCT02555657] and atezolizumab [ClinicalTrials.gov identifier: NCT03125902] in metastatic TNBC have been initiated. However, these trials exclude active CNS metastases, and are therefore unable to address the efficacy of ICIs on BM. We summarize the currently available prospective trials of ICI for patients with BM from other solid tumors in Table 4.

A systematic review of 13914 patients found the highest incidence of tumor-infiltrating lymphocytes of at least 50% both in TNBC (20%, range 4–37%) and HER-2 positive BC (16%, range 11–24%),$^{124}$ suggesting that proper modulation of the tumor microenvironment could boost antitumor activity of ICIs. Recent approaches have focused on the role of RT in this process, discussed further in the following.

**Combined approach of systemic therapies with RT**

The BBB is a critical obstacle to the efficacy of systemic treatments for BM, and researchers have explored mechanical and chemical methods to overcome this. One approach includes inducing transient opening of the BBB using a hyperosmolar solution.$^{125}$ Since September 2019, a study [ClinicalTrials.gov identifier: NCT03714243] of BBB disruption using magnetic-resonance-imaging-guided focused ultrasound began recruiting patients with HER2-positive BM at Sunnybrook Health Sciences Centre in Canada. Among several approaches to weakening the BBB, we will focus on studies using RT. For local treatment, addition of systemic treatment may help eradicate subclinical micrometastases and act as a radiosensitizer.

Sorafenib, an oral multi-targeted TKI, administered concurrently with WBRT or SRS in BM from solid tumors, including BC, was safe and tolerated in a phase I study.$^{126,127}$ A phase I study of HER2-positive BM treated with laptatinib in combination with WBRT followed by trastuzumab did not meet the prespecified feasibility criteria due to toxicity.$^{128}$ However, the high volumetric CNS ORR (79%, 95% CI 59–92) suggested this treatment strategy could be used in future studies. Accrual of a randomized phase II study has completed (RTOG 1119) [ClinicalTrials.gov identifier: NCT01622868], in which patients with unirradiated HER2-positive BM were randomized to WBRT/SRS with or without laptatinib (Table 2). The phase I REBECA study of 19 patients with untreated BM from solid tumors ($n = 13$ with BC) was performed to identify the recommended phase II bevacizumab dose when combined with WBRT (30 Gy/15 fractions) from day 15.$^{129}$ The regimen of 15 mg/kg bevacizumab for three cycles, with 2-week intervals, was deemed most appropriate, and 10 patients across all dose levels experienced an objective response per RECIST 1.1. Paradoxically, these synergistic effects might be explained by the fact that bevacizumab-induced vascular normalization before WBRT might reduce the hypoxic portion of tumors, leading to enhanced radiosensitivity rather than BBB disruption. Previous findings demonstrating that BEEP resulted in high CNS ORR$^{79}$ initiated a phase II randomized study [ClinicalTrials.gov identifier: NCT02185352], in which patients with WBRT-untreated BM not suitable for surgery or SRS were randomized into induction BEEP followed by WBRT (30 Gy/10 fractions) or WBRT alone (Table 2). In addition to BBB disruption, RT plays a crucial role in immuno-oncology by engaging antigen-specific immune responses, which serves as the rationale for RT and immunotherapy combinations.$^{130}$ The ICI and SRS combination has been largely investigated for BM in melanoma, and several retrospective studies have shown promising results.$^{131-133}$ The largest meta-analysis assessing impact of combination treatment on BM from solid tumors (mainly melanoma) reported that concurrent ICI and SRS improved OS (64.6% versus 51.6%; $p < 0.001$) and regional brain control (38.1% versus 12.3%; $p = 0.049$) at 1 year compared with nonconcurrent therapy.$^{134}$ Local control rates marginally differ between the two groups (89.2% versus 67.8%; $p = 0.09$), and incidence of radionecrosis was 5.3%. In recent years, three phase I or II studies have been launched to test the efficacy and safety of this innovative regimen in BM in BC: atezolizumab [ClinicalTrials.gov identifier: NCT03483012], pembrolizumab [ClinicalTrials.gov identifier: NCT03449238], and nivolumab [ClinicalTrials.gov identifier: NCT02185352].
NCT03807765], all concurrently administered with RT. More information about these trials is detailed in Table 2.

Another consideration when combining RT with systemic therapy is the timing of RT. SRS is highly effective when used concurrently in combination with ICI. In terms of WBRT, a phase I randomized study [ClinicalTrials.gov identifier: NCT02135159] examined the optimal sequence of T-DM1 in HER2-positive BM treatment: T-DM1 after, before, during and after, or concomitant with WBRT, respectively (Table 2); the trial is complete and awaiting results, which will likely inform the design of subsequent clinical trials.

Conclusion
Although cancer treatments have evolved in recent decades, effective treatments for BM are lacking. In patients with BM from BC, especially HER2-positive and TNBC, BM is the leading cause of mortality. Therefore, new treatment strategies for BM are an unmet clinical need.

Traditionally, local treatment for BM is most common, although recently, several innovative systemic therapies are being investigated. However, although BM is frequent in patients with BC, there is insufficient evidence to support established treatment strategies due to a lack of phase III randomized trials. In addition, given variation in biological features and intracranial failure patterns in different tumor subtypes, treatment for BM will likely have to be designed for each tumor molecular subtype. In recent years, treatment combinations with different systemic agents or integration of local therapy have shown outstanding results compared with monotherapy, demonstrating that comprehensive investigations of multimodal approaches are needed in treatment for BM from BC.

Molecular characterization of BMs before treatment may also be necessary, as treatment may be based on tumor molecular subtype; however, there are many challenges with this approach. Therefore, there is also a need for research on alternative techniques for predicting tumor molecular subtypes with high precision using brain imaging or circulating tumor deoxyribonucleic acid in serum or cerebrospinal fluid. In addition, research on the prevention, reduction, or management of side effects caused by treatment will be needed to increase patient tolerance.

Much progress on BM treatment strategies has been made in recent years, but many gaps still remain to be filled before a standard-of-care regimen is established. On the other hand, although not covered in this paper, screening for BC in women should be actively performed to improve PFS and OS by diagnosing BC at an early stage, and we have to pursue further investigations to find out proper neoadjuvant and adjuvant treatments along with complete surgical resection of BC to reduce locoregional recurrences and/or distant metastases. Early detection of asymptomatic BM through imaging follow up of the brain is essential in metastatic HER2-positive and TNBC patients, who are susceptible to the development of BM. Studies on proper intervals of imaging follow up are also important issues. However, BM screening in non-metastatic patients could not yet be justified, unlike patients with lung cancer. These strategies on early detection of BC and secondary prevention of BM might provide promising treatment outcomes and patients’ quality of life.

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ORCID iD
In Ah Kim https://orcid.org/0000-0001-9838-5399

References
1. Lin NU, Bellon JR and Winer EP. CNS metastases in breast cancer. J Clin Oncol 2004; 22: 3608–3617.
2. Tabouret E, Chinot O, Metellus P, et al. Recent trends in epidemiology of brain metastases: an overview. Anticancer Res 2012; 32: 4655–4662.
3. Heitz F, Harter P, Lueck HJ, et al. Triple-negative and HER2-overexpressing breast cancers exhibit an elevated risk and an earlier
occurrence of cerebral metastases. Eur J Cancer 2009; 45: 2792–2798.

4. Sperduto PW, Kased N, Roberge D, et al. The effect of tumor subtype on the time from primary diagnosis to development of brain metastases and survival in patients with breast cancer. J Neurooncol 2013; 112: 467–472.

5. Cagney DN, Lamba N, Montoya S, et al. Breast cancer subtype and intracranial recurrence patterns after brain-directed radiation for brain metastases. Breast Cancer Res Treat 2019; 176: 171–179.

6. Darlix A, Louvel G, Fraisse J, et al. Impact of breast cancer molecular subtypes on the incidence, kinetics and prognosis of central nervous system metastases in a large multicentre real-life cohort. Br J Cancer 2019; 121: 991–1000.

7. Komorowski AS, Warner E, MacKay HJ, et al. Incidence of breast metastases in nonmetastatic and metastatic breast cancer: is there a role for screening? Clin Breast Cancer. 2020; 20: e54–e64.

8. Witzel I, Oliveira-Ferrer L, Pantel K, et al. Breast cancer brain metastases: biology and new clinical perspectives. Breast Cancer Res 2016; 18: 1–9.

9. Soni A, Ren Z, Hameed O, et al. Breast cancer subtypes predispose the site of distant metastases. Am J Clin Pathol 2015; 143: 471–478.

10. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol 2010; 28: 3271–3277.

11. Smid M, Wang Y, Zhang Y, et al. Subtypes of breast cancer show preferential site of relapse. Cancer Res 2008; 68: 3108–3114.

12. Lai R, Dang CT, Malkin MG, et al. The risk of central nervous system metastases after trastuzumab therapy in patients with breast carcinoma. Cancer 2004; 101: 810–816.

13. Lin NU, Claus E, Sohl J, et al. Sites of distant recurrence and clinical outcomes in patients with metastatic triple-negative breast cancer. Cancer 2008; 113: 2638–2645.

14. Quigley MR, Fukui O, Chew B, et al. The shifting landscape of metastatic breast cancer to the CNS. Neurosurg Rev 2013; 36: 377–382.

15. Jeon W, Jang BS, Jeon SH, et al. Analysis of survival outcomes based on molecular subtypes in breast cancer brain metastases: a single institutional cohort. Breast J 2018; 24: 920–926.

16. Kim JS, Kim K, Jung W, et al. Survival outcomes of breast cancer patients with brain metastases: a multicenter retrospective study in Korea (KROG 16–12). Breast 2020; 49: 41–47.

17. Niikura N, Hayashi N, Masuda N, et al. Treatment outcomes and prognostic factors for patients with brain metastases from breast cancer of each subtype: a multicenter retrospective analysis. Breast Cancer Res Treat 2014; 147: 103–112.

18. Vogel CL, Cobleigh MA, Tripathy D, et al. Efficacy and safety of trastuzumab as a single agent in first-line treatment of HER2-overexpressing metastatic breast cancer. J Eur J Cancer 2002; 20: 719–726.

19. Bendell JC, Domchek SM, Burstein HJ, et al. Central nervous system metastases in women who receive trastuzumab-based therapy for metastatic breast carcinoma. Cancer 2003; 97: 2972–2977.

20. Clayton AJ, Danson S, Jolly S, et al. Incidence of cerebral metastases in patients treated with trastuzumab for metastatic breast cancer. Br J Cancer 2004; 91: 639–643.

21. Musolino A, Ciccocollo L, Panebianco M, et al. Multifactorial central nervous system recurrence susceptibility in patients with HER2-positive breast cancer: epidemiological and clinical data from a population-based cancer registry study. Cancer 2011; 117: 1837–1846.

22. Smedby KE, Brandt L, Bäcklund ML, et al. Brain metastases admissions in Sweden between 1987 and 2006. Br J Cancer 2009; 101: 1919–1924.

23. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. N Engl J Med 1990; 322: 494–500.

24. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. Lancet Oncol 2009; 10: 1037–1044.

25. Mehta M. The dandelion effect: treat the whole lawn or weed selectively? J Clin Oncol 2011; 29: 121–124.

26. Tsao MN, Rades D, Wirth A, et al. Radiotherapeutic and surgical management for newly diagnosed brain metastasis(es): an American Society for Radiation Oncology evidence-based guideline. Pract Radiat Oncol 2012; 2: 210–225.

27. National Comprehensive Cancer Network. Central nervous system cancers version 1. 2020, www.nccn.org/professionals/physician_gls/pdf/cns.pdf (2020, accessed 4 April 2020).

28. Arvold ND, Lee EQ, Mehta MP, et al. Updates in the management of brain metastases. Neuro Oncol 2016; 18: 1043–1065.
29. Mahmoud-Ahmed AS, Suh JH, Lee SY, et al. Results of whole brain radiotherapy in patients with brain metastases from breast cancer: a retrospective study. *Int J Radiat Oncol Biol Phys* 2002; 54: 810–817.

30. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA* 2006; 295: 2483–2491.

31. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011; 29: 134–141.

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

33. Sahgal A, Aoyama H, Kocher M, et al. Phase 3 trials of stereotactic radiosurgery with or without whole-brain radiation therapy for 1 to 4 brain metastases: individual patient data meta-analysis. *Int J Radiat Oncol Biol Phys* 2015; 91: 710–717.

34. Sahgal A, Larson D and Knisely J. Stereotactic radiosurgery alone for brain metastases. *Lancet Oncol* 2015; 16: 249–250.

35. Chao ST, De Salles A, Hayashi M, et al. Stereotactic radiosurgery in the management of limited (1-4) brain metastases: systematic review and international stereotactic radiosurgery society practice guideline. *Neurosurgery* 2018; 83: 345–353.

36. Lin NU, Eierman W, Greil R, et al. Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. *J Neurooncol* 2011; 105: 613–620.

37. Cortes J, Dieras V, Ro J, et al. Afatinib alone or afatinib plus vinorelbine versus investigator’s choice of treatment for HER2-positive breast cancer with progressive brain metastases after trastuzumab, lapatinib, or both (LUX-Breast 3): a randomised, open-label, multicentre, phase 2 trial. *Lancet Oncol* 2015; 16: 1700–1710.

38. Li J, Bentzen SM, Renschler M, et al. Regression after whole-brain radiation therapy for brain metastases correlates with survival and improved neurocognitive function. *J Clin Oncol* 2007; 25: 1260–1266.

39. Gondi V, Pugh SL, Tome WA, et al. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 2014; 32: 3810–3816.

40. Tsai PF, Yang CC, Chuang CG, et al. Hippocampal dosimetry correlates with the change in neurocognitive function after hippocampal sparing during whole brain radiotherapy: a prospective study. *Radiat Oncol* 2015; 10: 253.

41. Gondi V, Deshmukh S, Brown PD, et al. NRG oncology CC001: a phase III trial of hippocampal avoidance (HA) in addition to whole-brain radiotherapy (WBRT) plus memantine to preserve neurocognitive function (NCF) in patients with brain metastases (BM). *J Clin Oncol* 2019; 37(Suppl. 15): Abstract 2009.

42. Ou D, Cao L, Xu C, et al. Upfront brain radiotherapy may improve survival for unfavorable prognostic breast cancer brain metastasis patients with Breast-GPA 0-2.0. *Breast J* 2019; 25: 1134–1142.

43. Sahgal A, Ruschin M, Ma L, et al. Stereotactic radiosurgery alone for multiple brain metastases? A review of clinical and technical issues. *Neuro Oncol* 2017; 19: ii2–ii15.

44. Hughes RT, Masters AH, McTyre ER, et al. Initial SRS for patients with 5 to 15 brain metastases: results of a multi-institutional experience. *Int J Radiat Oncol Biol Phys* 2019; 104: 1091–1098.

45. Yamamoto M, Serizawa T, Shuto T, et al. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014; 15: 387–395.

46. Baliga S, Garg MK, Fox J, et al. Fractionated stereotactic radiation therapy for brain metastases: a systematic review with tumour control probability modelling. *Br J Radiol* 2017; 90: 20160666.

47. Masucci GL. Hypofractionated radiation therapy for large brain metastases. *Front Oncol* 2018; 8: 379.

48. Zhang C and Yu D. Advances in decoding breast cancer brain metastasis. *Cancer Metastasis Rev* 2016; 35: 677–684.
50. Shah N, Mohammad AS, Saralkar P, et al. Investigational chemotherapy and novel pharmacokinetic mechanisms for the treatment of breast cancer brain metastases. *Pharmacol Res* 2018; 132: 47–68.

51. Spriggs DR and Gounder MM. Inclusion of patients with brain metastases in phase I trials: an unmet need. *Clin Cancer Res* 2011; 17: 3855–3857.

52. Morikawa A, Jhaveri K and Seidman AD. Clinical trials for breast cancer with brain metastases: challenges and new directions. *Curr Breast Cancer Rep* 2013; 5: 293–301.

53. Romond EH, Perez EA, Bryant J, et al. Trastuzumab plus adjuvant chemotherapy for operable HER2-positive breast cancer. *N Engl J Med* 2005; 353: 1673–1684.

54. Pestalozzi BC and Brignoli S. Trastuzumab in metastatic breast cancer. *Breast Cancer Rep* 2013; 19: 724–734.

55. Swain SM, Baselga J, Kim SB, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. *N Engl J Med* 2015; 372: 699–711.

56. Swain SM, Baselga J, Miles D, et al. Incidence of central nervous system metastases in patients with HER2-positive metastatic breast cancer treated with pertuzumab, trastuzumab, and docetaxel: results from the randomized phase III study CLEOPATRA. *Ann Oncol* 2014; 25: 116–121.

57. Lin NU, Stein A, Nicholas A, et al. Planned interim analysis of PATRICIA: an open-label, single-arm, phase II study of pertuzumab (P) with high-dose trastuzumab (H) for the treatment of central nervous system (CNS) progression post radiotherapy (RT) in patients (pts) with HER2-positive meta. *J Clin Oncol* 2017; 35(Suppl. 15): Abstract 2074.

58. Rusnak DW, Mullin RJ, Alligood KJ, et al. The characterization of novel, dual ErbB-2/EGFR, tyrosine kinase inhibitors: potential therapy for cancer. *Cancer Res* 2001; 61: 7196–7203.

59. Lin NU, Diéras V, Paul D, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. *Clin Cancer Res* 2009; 15: 1452–1459.

60. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol* 2013; 14: 64–71.

61. Morikawa A, De Stanchina E, Pentsova E, et al. Phase I study of intermittent high-dose lapatinib alternating with capecitabine for HER2-positive breast cancer patients with central nervous system metastases. *Clin Cancer Res* 2019; 1: 3784–3792.

62. De Azambuja E, Zardavas D, Lemort M, et al. Phase I trial combining temozolomide plus lapatinib for the treatment of brain metastases in patients with HER2-positive metastatic breast cancer: the LAPTEM trial. *Ann Oncol* 2013; 24: 2985–2989.

63. Rabindran SK, Discafani CM, Rosfjord EC, et al. Antitumor activity of HKI-272, an orally active, irreversible inhibitor of the HER-2 tyrosine kinase. *Cancer Res* 2004; 64: 3958–3965.

64. Freedman RA, Gelman RS, Wefel JS, et al. Translational breast cancer research consortium (TBCRC) 022: a phase II trial of neratinib for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol* 2016; 34: 945–952.

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

66. Saura C, Oliveira M, Feng YH, et al. Neratinib + capecitabine versus lapatinib + capecitabine in patients with HER2+ metastatic breast cancer previously treated with ≥2 HER2-directed regimens: findings from the multinational, randomized, phase III NALA trial. *J Clin Oncol* 2019; 37(Suppl. 15): Abstract 1002.

67. Li D, Ambrogio L, Shimamura T, et al. BIBW2992, an irreversible EGFR/HER2 inhibitor highly effective in preclinical lung cancer models. *OncoGene* 2008; 27: 4702–4711.

68. Moulder SL, Borges VF, Baetz T, et al. Phase I study of ONT-380, a HER2 inhibitor, in patients with HER2+-advanced solid tumors, with an expansion cohort in HER2+ metastatic breast cancer (MBC). *Clin Cancer Res* 2017; 23: 3529–3536.

69. Murthy R, Borges VF, Conlin A, et al. Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. *Lancet Oncol* 2018; 19: 880–888.
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71. Murthy RK, Loi S, Okines A, et al. Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. *N Engl J med.* 2020; 13: 597–609.

72. Metzger O, Barry W, Krop I, et al. Phase I dose-escalation trial of ONT-380 in combination with trastuzumab in patients (pts) with HER2+ breast cancer brain metastases. *Cancer Res* 2017; 77(Suppl. 4): Abstract P1-12-04.

73. Borges VF, Ferrario C, Aucoin N, et al. Tucatinib combined with ado-Trastuzumab emtansine in advanced ERBB2/HER2-positive metastatic breast cancer: a phase Ib clinical trial. *JAMA Oncol* 2018; 4: 1214–1220.

74. Zhu Y, Li L, Zhang G, et al. Metabolic characterization of pyrotinib in humans by ultra-performance liquid chromatography/quadrupole time-of-flight mass spectrometry. *J Chromatogr B Analyt Technol Biomed Life Sci* 2016; 1033–1034: 117–127.

75. Jiang Z, Yan M, Hu X, et al. Pyrotinib combined with capecitabine in women with HER2+ metastatic breast cancer previously treated with trastuzumab and taxanes: a randomized phase III study. *J Clin Oncol* 2019; 37(Suppl. 15): Abstract 1001.

76. MacPherson IR, Spiropoulos P, Rafii S, et al. A phase I/II study of epertinib plus trastuzumab with or without chemotherapy in patients with HER2-positive metastatic breast cancer. *Breast Cancer Res Treat* 2019; 117–127.

77. Dickson PV, Hamner JB, Sims TL, et al. Bevacizumab-induced transient remodeling of the vasculature in neuroblastoma xenografts results in improved delivery and efficacy of systemically administered chemotherapy. *Clin Cancer Res* 2007; 13: 3942–3950.

78. Lin NU, Gelman RS, Younger JW, et al. Phase II trial of carboplatin (C) and bevacizumab (BEV) in patients (pts) with breast cancer brain metastases (BCBM). *J Clin Oncol* 2013; 31 (suppl. 15): Abstract 513.

79. Lu YS, Chen TWW, Lin CH, et al. Bevacizumab preconditioning followed by etoposide and cisplatin is highly effective in treating brain metastases of breast cancer progressing from whole-brain radiotherapy. *Clin Cancer Res* 2015; 21: 1851–1858.

80. Wu PF, Lin CH, Kuo CH, et al. A pilot study of bevacizumab combined with etoposide and cisplatin in breast cancer patients with leptomeningeal carcinomatosis. *BMC Cancer* 2015; 15: 1–7.

81. Klempner SJ, Borghesi A, Hakimian B, et al. Intracranial Activity of Cabozantinib in MET Exon 14-Positive NSCLC with Brain Metastases. *J Thoracic Oncol* 2017; 12: 152–156.

82. Peverelli G, Raimondi A, Ratta R, et al. Cabozantinib in renal cell carcinoma with brain metastases: safety and efficacy in a real-world population. *Clin Genitourin Cancer* 2019; 17: 291–298.

83. Leone JP, Duda DG, Hu J, et al. A phase II study of cabozantinib alone or in combination with trastuzumab in breast cancer patients with brain metastases. *Breast Cancer Res Treat* 2019; 179: 113–123.

84. Gallardo A, Lerma E, Escuin D, et al. Increased signalling of EGFR and IGF1R, and deregulation of PTEN/PI3K/Akt pathway are related with trastuzumab resistance in HER2 breast carcinomas. *Br J Cancer* 2012; 106: 1367–1373.

85. Van Swearingen AED, Siegel MB, Deal AM, et al. LCCC 1025: a phase II study of everolimus, trastuzumab, and vinorelbine to treat progressive HER2-positive breast cancer brain metastases. *Breast Cancer Res Treat* 2018; 171: 637–648.

86. Buchanan CM, Lee KL and Shepherd PR. For better or worse: the potential for dose limiting the on-target toxicity of PI 3-kinase inhibitors. *Biomolecules* 2019; 9: 402.

87. Bendell JC, Rodon J, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* 2016; 17: 425–439.

88. Cristofanilli M, Turner NC, Bondarenko I, et al. Fulvestrant plus palbociclib versus fulvestrant plus placebo for treatment of hormone-receptor-positive, HER2-negative metastatic breast cancer that progressed on previous endocrine therapy (PALOMA-3): final analysis of the multicentre, double-blind, phase 3 randomised controlled trial. *Lancet Oncol* 2016; 17: 425–439.

89. Hortobagyi GN, Stemmer SM, Burris HA, et al. Ribociclib as first-line therapy for HR-positive, advanced breast cancer. *N Engl J Med* 2016; 375: 1738–1748.

90. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol* 2017; 35: 3638–3646.

91. Nguyen LV, Searle K and Jerzak KJ. Central nervous system-specific efficacy of CDK4/6 inhibitors in randomized controlled trials for metastatic breast cancer. *Oncotarget* 2019; 10: 6317–6322.
92. Anders CK, le Rhun E, Bachelot TD, et al. A phase II study of abemaciclib in patients (pts) with brain metastases (BM) secondary to HR+, HER2- metastatic breast cancer (MBC). J Clin Oncol 2019; 37(Suppl. 15): Abstract 1017.

93. Matutino A, Amaro C and Verma S. CDK4/6 inhibitors in breast cancer: beyond hormone receptor-positive HER2-negative disease. Ther Adv Med Oncol 2018; 10: 17583591881834.

94. Anders C, Deal AM, Abramson V, et al. TBCRC 018: phase II study of iniparib in combination with irinotecan to treat progressive triple negative breast cancer brain metastases. Breast Cancer Res Treat 2014; 146: 557–566.

95. Liu X, Shi Y, Maag DX, et al. Iniparib nonselectively modifies cysteine-containing proteins in tumor cells and is not a bona fide PARP inhibitor. Clin Cancer Res 2012; 18: 510–523.

96. Pascual T, Gonzalez-Farre B, Teisidó C, et al. Significant clinical activity of olaparib in a somatic BRCA1-mutated triple-negative breast cancer with brain metastasis. JCO Precis Oncol. Epub ahead of print 7 June 2019. DOI: 10.1200/po.19.00012.

97. Deeken JF and Löscher W. The blood-brain barrier and cancer: transporters, treatment, and Trojan horses. Clin Cancer Res 2007; 13: 1663–1674.

98. Demene M, Currie JC, Bertrand Y, et al. Involvement of the low-density lipoprotein receptor-related protein in the transcytosis of the brain delivery vector Angiopep-2. J Neurochem 2008; 106: 1534–1544.

99. Hoch U, Staschen CM, Johnson RK, et al. Nonclinical pharmacokinetics and activity of etirinotecan pegol (NKTR-102), a long-acting topoisomerase 1 inhibitor, in multiple cancer models. Cancer Chemother Pharmacol 2014; 74: 1125–1137.

100. Ibrahim NK, Tang SC, Brenner AJ, et al. A phase II, open-label, multi-center study of ANG1005, a novel brain-penetrant peptide-drug conjugate, in breast cancer patients with recurrent CNS metastases. Cancer Res 2017; 77(Suppl. 4): Abstract P1-12-01.

101. Chabot GG, Abigerges D, Catimel G, et al. Population pharmacokinetics and pharmacodynamics of irinotecan (CPT-11) and active metabolite SN-38 during phase I trials. Ann Oncol 1995; 6: 141–151.

102. Perez EA, Awada A, O'Shaughnessy J, et al. Etirinotecan pegol (NKTR-102) versus treatment of physician's choice in women with advanced breast cancer previously treated with an anthracycline, a taxane, and capecitabine (BEACON): a randomised, open-label, multicentre, phase 3 trial. Lancet Oncol 2015; 16: 1556–1568.

103. Cortés J, Rugo HS, Awada A, et al. Prolonged survival in patients with breast cancer and a history of brain metastases: results of a preplanned subgroup analysis from the randomized phase III BEACON trial. Breast Cancer Res Treat 2017; 165: 329–341.

104. Seidman AD, Schwartzberg LS, Gudena VK, et al. Activity of tesetaxel, an oral taxane, given as a single-agent in patients (Pts) with HER2-, hormone receptor + (HR+) locally advanced or metastatic breast cancer (MBC) in a phase 2 study. J Clin Oncol 2018; 36(Suppl. 15): Abstract 1042.

105. Peereboom DM, Murphy C, Ahluwalia MS, et al. Phase II trial of patupilone in patients with brain metastases from breast cancer. Neuro Oncol 2018; 16: 579–583.

106. Melisko ME, Assefa M, Hwang J, et al. Phase II study of irinotecan and temozolomide in breast cancer patients with progressing central nervous system disease. Breast Cancer Res Treat 2019; 177: 401–408.

107. Darwin P, Toor SM, Sasidharan Nair V, et al. Immune checkpoint inhibitors: recent progress and potential biomarkers. Exp Mol Med 2018; 50: 1–11.

108. Di Giacomo AM, Valente M, Cerase A, et al. Immunotherapy of brain metastases: breaking a “dogma”. J Exp Clin Cancer Res 2019; 38: 1–10.

109. Rittmeyer A, Barlesi F, Waterkamp D, et al. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. Lancet 2017; 389: 255–265.

110. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. Lancet Oncol 2012; 13: 459–465.

111. Di Giacomo AM, Asciento PA, Pilla L, et al. Ipilimumab and fotemustine in patients with advanced melanoma (NIBIT-M1): an open-label, single-arm phase 2 trial. Lancet Oncol 2012; 13: 879–886.

112. Di Giacomo AM, Asciento PA, Queirolo P, et al. Three-year follow-up of advanced melanoma patients who received ipilimumab plus fotemustine in the Italian network for tumor biotherapy (NIBIT)-M1 phase II study. Ann Oncol 2015; 26: 798–803.
113. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med* 2018; 379: 722–730.

114. Tawbi HAH, Forsyth PAJ, Hodi FS, et al. Efficacy and safety of the combination of nivolumab (NIVO) plus ipilimumab (IPI) in patients with symptomatic melanoma brain metastases (CheckMate 204). *J Clin Oncol* 2019; 37(Suppl. 15): Abstract 9501.

115. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol* 2018; 19: 672–681.

116. Emamekhoo H, Olsen M, Carthon BC, et al. Safety and efficacy of nivolumab plus ipilimumab (NIVO+IPI) in patients with advanced renal cell carcinoma (aRCC) with brain metastases: interim analysis of CheckMate 920. *J Clin Oncol* 2019; 37(Suppl. 1): Abstract 4517.

117. Goldman JW, Crino L, Vokes EE, et al. Nivolumab (nivo) in patients (pts) with advanced (adv) NSCLC and central nervous system (CNS) metastases (mets). *J Clin Oncol* 2016; 34(Suppl. 15): Abstract 9038.

118. Flippot R, Dalban C, Laguerre B, et al. Safety and efficacy of nivolumab in brain metastases from renal cell carcinoma: results of the GETUG-AFU 26 NIVOREN multicenter phase II study. *J Clin Oncol* 2019; 37: 2008–2016.

119. Kluger HM, Chiang V, Mahajan A, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. *J Clin Oncol* 2019; 37: 52–60.

120. Goldberg SB, Gettinger SN, Mahajan A, et al. Durability of brain metastasis response and overall survival in patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab. *J Clin Oncol* 2018; 36(Suppl. 15): Abstract 2009.

121. Goldberg SB, Schalper KA, Gettinger SN, et al. Pembrolizumab for management of patients with NSCLC and brain metastases: long-term results and biomarker analysis from a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. Epub ahead of print 3 April 2020. DOI: 10.1016/S1470-2045(20)30111-X.

122. Schmid P, Adams S, Hugo HS, et al. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med* 2018; 379: 2108–2121.

123. Kenilworth; Merck. Merck’s Keytruda® (pembrolizumab) in combination with chemotherapy met primary endpoint of progression-free survival (PFS) as first-line treatment for metastatic triple-negative breast cancer (mTNBC), https://pipelinereview.com/index.php/2020021273778/Antibodies/Mercks-KEYTRUDA-pembrolizumab-in-Combination-with-Chemotherapy-Met-Primary-Endpoint-of-Progression-Free-Survival-PFS-as-First-Line-Treatment-for-Metastatic-Triple-Negative-Bre. html (2020, accessed 6 April 2020)

124. Stanton SE, Adams S and Disis ML. Variation in the incidence and magnitude of tumor-infiltrating lymphocytes in breast cancer subtypes: a systematic review. *JAMA Oncol* 2016; 2: 1354–1360.

125. Gumerlock MK, Belshe BD, Madsen R, et al. Osmotic blood-brain barrier disruption and chemotherapy in the treatment of high grade malignant glioma: patient series and literature review. *J Neurooncol* 1992; 12: 33–46.

126. Morikawa A, Grkovski M, Patil S, et al. MLTI-02. A phase I trial of sorafenib with whole brain radiotherapy (WBRT) in breast cancer patients with brain metastases and a correlative FLT-PET brain imaging study in patients receiving WBRT +/- sorafenib. *Neurooncol Adv* 2019; 1(Suppl. 1): i14.

127. Arneson K, Mondschein J, Stavas M, et al. A phase I trial of concurrent sorafenib and stereotactic radiosurgery for patients with brain metastases. *J Neurooncol* 2017; 133: 435–442.

128. Lin NU, Freedman RA, Ramakrishna N, et al. A phase I study of lapatinib with whole brain radiotherapy in patients with human epidermal growth factor receptor 2 (HER2)-positive breast cancer brain metastases. *Breast Cancer Res Treat* 2013; 142: 405–414.

129. Lévy C, Allouache D, Lacroix J, et al. REBEOCA: a phase I study of bevacizumab and whole-brain radiation therapy for the treatment of brain metastasis from solid tumours. *Ann Oncol* 2014; 25: 2231–2236.

130. Sharabi AB, Lim M, DeWeese TL, et al. Radiation and checkpoint blockade immunotherapy: radiosensitisation and potential mechanisms of synergy. *Lancet Oncol* 2015; 16: e498–e509.

131. Kiess AP, Wolchok JD, Barker CA, et al. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. *Int J Radiat Oncol Biol Phys* 2015; 92: 368–375.
132. Murphy B, Walker J, Bassale S, et al. Concurrent radiosurgery and immune checkpoint inhibition improving regional intracranial control for patients with metastatic melanoma. *Am J Clin Oncol* 2019; 42: 253–257.

133. Qian JM, Yu JB, Kluger HM, et al. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. *Cancer* 2016; 122: 3051–3058.

134. Lehrer EJ, Peterson J, Brown PD, et al. Treatment of brain metastases with stereotactic radiosurgery and immune checkpoint inhibitors: an international meta-analysis of individual patient data. *Radiother Oncol* 2019; 130: 104–112.