Systemic therapy of brain metastases: non–small cell lung cancer, breast cancer, and melanoma

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Abstract

Brain metastases (BM) occur frequently in many cancers, particularly non–small cell lung cancer (NSCLC), breast cancer, and melanoma. The development of BM is associated with poor prognosis and has an adverse impact on survival and quality of life. Commonly used therapies for BM such as surgery or radiotherapy are associated with only modest benefits. However, recent advances in systemic therapy of many cancers have generated considerable interest in exploration of those therapies for treatment of intracranial metastases.

This review discusses the epidemiology of BM from the aforementioned primary tumors and the challenges of using systemic therapies for metastatic disease located within the central nervous system. Cumulative data from several retrospective and small prospective studies suggest that molecularly targeted systemic therapies may be an effective option for the treatment of BM from NSCLC, breast cancer, and melanoma, either as monotherapy or in conjunction with other therapies. Larger prospective studies are warranted to further characterize the efficacy and safety profiles of these targeted agents for the treatment of BM.

Keywords: Brain metastases | breast cancer | blood-brain barrier | melanoma | non–small cell lung cancer

Involvement of the central nervous system (CNS) is a complication of many cancers. Brain metastases (BM) from systemic malignancies account for the majority of intracranial cancers, with an estimated incidence rate of 8.3 to 11.0 per 100,000 as compared with an incidence rate of 6.6 per 100,000 for all primary malignant CNS tumors. The development of BM is usually associated with poor prognosis and significant adverse effects on survival and quality of life. Overall, BM are associated with a low 2-year survival rate (8%) and a high burden of neurologic symptoms including headaches, nausea and vomiting, focal motor deficits, cognitive decline, delirium, and seizures.

BM affect 8%–10% of all cancer patients and 40% of patients with metastatic cancer. The majority of BM originate from lung cancer (40%–50%), breast cancer (15%–25%), and melanoma (5%–20%). BM predominate in the cerebral hemispheres (80%) followed by the cerebellum (15%) and brainstem (5%), a pattern of distribution reflective of proportional blood flow to these respective regions. The incidence of BM is believed to be increasing, likely resulting from longer patient survival due to more effective systemic therapies for the primary cancer and the increased use of neuroimaging in neurologically asymptomatic patients.

Treatment options for BM are limited and suboptimal. Historically, the mainstay of therapy has been local treatments such as surgery or radiation therapy (RT) (ie, whole brain radiation therapy [WBRT], stereotactic radiosurgery [SRS], or stereotactic radiation therapy [SRT]). The choice of local therapy is generally guided by the number and location of BM, the extent and prognosis of systemic disease, and the performance status of the patient. Patients with minimal systemic disease, good performance status, and solitary brain
metastasis in a noneloquent location of the brain are often treated with surgical resection followed by RT. Patients with minimal systemic disease, good performance, and oligometastatic disease in the brain are generally treated with SRT and deferred WBRT. In contrast, patients with greater metastatic burden are usually treated with WBRT despite a lack of randomized trials showing effectiveness of WBRT compared with best standard care; there is an emerging perspective, however, that these patients can be treated with SRS, especially when effective systemic therapy may be available. In a select group of patients (<15% of all patients with BM), aggressive local treatment can prolong survival to ≥12 months. The evolving classification of specific molecular subtypes within most cancers (eg, hormone receptor status in breast cancer or anaplastic lymphoma kinase [ALK] rearrangement in non–small cell lung cancer [NSCLC]) will likely alter treatment of BM based on improved prognostication linked to specific tumor subtypes.

Historically, the role of systemic therapy in the treatment of BM has been limited by concerns regarding limited penetration across the blood-brain barrier (BBB), rapid efflux from brain, or intrinsic chemotherapy resistance resulting from multiple prior lines of therapy. Furthermore, patients with symptomatic or uncontrolled BM have generally been excluded from randomized controlled trials of systemic pharmacotherapies. Additionally, CNS outcome measures were often not reported separately from systemic efficacy outcomes. However, novel targeted therapies have substantially improved systemic disease control and survival in molecularly defined cancer populations, which have generated considerable interest in the investigation of these therapies to complement or even replace local therapies for treatment of BM. Although the constraints on parenchymal brain drug delivery also apply to targeted therapies, these agents are increasingly being selected for further study in patients with BM based, in part, on their CNS penetration.

The objective of this review is to summarize the efficacy of emerging systemic therapies, especially targeted therapies and immunotherapies, for the treatment of BM, focusing on the 3 cancers (NSCLC, breast cancer, and melanoma) that most often metastasize to the CNS.

Targeting Brain Metastases: Challenges

When employed in treating BM, a systemic therapy must traverse the BBB, the blood-cerebrospinal fluid (CSF) barrier, and the blood-tumor barrier in sufficient concentration to enable its therapeutic effect (Fig. 1). These various barriers render the brain and CSF inaccessible to most chemotherapeutic drugs because of large size (>150kDa), ionization, hydrophilicity, and/or protein-binding. Additionally, many of the small lipophilic molecules that cross the BBB and blood-tumor barriers can be exported from the brain by highly regulated transmembrane efflux pumps located in the endothelial vasculature of the CNS. Although BM may increase permeability to systemic drugs by disrupting the structural integrity of the BBB and blood-tumor barrier, this is usually not sufficient to achieve therapeutic levels of most drugs in the CNS. Dose escalation of systemically administered drugs (eg, high-dose methotrexate) is generally limited by systemic toxicity. Furthermore, subtherapeutic concentrations of anticancer drugs achieved in the brain may potentially contribute to acquired treatment resistance.

Brain Metastases from Non–small Cell Lung Cancer

Lung cancer, the most common cancer overall, has the highest incidence of BM among all cancers. Approximately 40%–50% of all CNS metastases arise from lung cancer (Table 1), and approximately half of all patients with NSCLC develop BM during the course of their disease. The median overall survival (OS) for patients with BM from NSCLC is 7 months per the Grade Prognostic Assessment (GPA) index. Fortunately, emerging systemic therapies may improve outcomes for this challenging subgroup of patients.

Non–small cell lung cancer is heterogeneous and composed of several molecular subtypes associated with specific driver oncopogens (Fig. 2); these molecular subtypes are characterized by different prognoses and responses to therapy. Recent advances in the treatment of NSCLC can be credited to improved understanding of the pathogenesis of these molecular subtypes. For example, 10%–35% of NSCLC tumors harbor a somatic activating mutation in the epidermal growth factor receptor (EGFR) gene. Patients with activating mutations in EGFR have overall response rates up to 85% and progression-free survival (PFS) as long as 13 months with the EGFR tyrosine kinase inhibitors (TKIs) gefitinib, erlotinib, or afatinib compared with cytotoxic chemotherapy (up to 38% and 7 mo, respectively). Rearrangement of ALK is observed in approximately 5% of the adenocarcinoma population and predicts a good overall response rate to ALKTKIs as with crizotinib (65%) versus cytotoxic chemotherapy (20%). Immune checkpoint inhibitors have also led to impressive durable responses in a subgroup of patients. All of these emerging therapies are increasingly proving to be effective in treating patients with BM.

Targeted Therapy with EGFR Tyrosine Kinase Inhibitors

Patients with EGFR-mutant NSCLC often develop multiple small BM with little peritumoral edema. Efficacy of EGFR TKIs in patients with EGFR-mutant NSCLC is well established; however, efficacy in patients with BM is not as clear because patients with symptomatic or uncontrolled BM were excluded from pivotal, randomized controlled trials. Consequently, data on the efficacy of TKI therapy in the CNS have been gleaned mostly from retrospective studies of those trials that enrolled patients with BM.

While the low molecular weight and nonpolar nature of TKIs permit passive diffusion across the BBB, many TKIs are substrates for efflux transporter proteins (Table 2).
Nevertheless, CSF concentrations of erlotinib, gefitinib, and afatinib exceed those required to inhibit growth of cells harboring EGFR mutations in vitro (Table 2). An early prospective study of 41 patients with unselected NSCLC BM treated with gefitinib resulted in 4 (10%) intracranial partial responses with a median duration of response of 13.5 months (Table 3).33,34 In another study of unselected patients, a 70% CNS response was observed with first-line erlotinib or gefitinib.35 These patients were mostly Asian, female never-smokers who had a high incidence of EGFR mutations; thus, the prevalence of mutation in this study was likely higher than the general NSCLC population.19

Data from other retrospective studies also suggest that patients with BM from EGFR-mutant NSCLC have better outcomes with either WBRT or TKI therapy than patients with BM from EGFR-wild-type NSCLC (Table 3).31,36,37 A retrospective analysis of 69 cases previously treated with erlotinib reported time to progression within the brain of 11.7 months for patients with EGFR mutations compared with 5.8 months for those with EGFR-wild-type or unassessed tumors, despite the fact that only 16% of patients with EGFR mutations had received WBRT versus 85% of those without the mutation (Table 3).38 Subsequent prospective phase 2 studies of patients with EGFR-mutant NSCLC indicated that TKI therapy provided intracranial responses of ≥75%.39,40 Despite an initial favorable intracranial response, patients often have CNS progression while maintaining systemic disease control on TKI therapy.41,42 A linear correlation is seen between between plasma and CSF concentrations of EGFR TKIs, suggesting that a higher dose may lead to higher CSF concentration and thereby potentially improve CNS disease response.41,43 For instance, in case reports and early phase clinical trials, a response as high as 81% has been reported with an erlotinib twice weekly pulse dose level of 600–1350mg.44 However, an independent,
In the small Crizotinib was the first ALK inhibitor approved 25%−46% of TNBC cases; 55%−75% of melanoma cases based on autopsy report. This observation can Table 3, 188 1 1 Osimertinib Similarly equivocal data have been Table 2 15%−25% of all BM, 46, 149 187 51 Despite the 3 46, ). Pooled analysis of a phase 3, 1 1 1 1 1 ≤50% of melanoma cases 50 35%−50% of NSCLC BM cases, 59 56 ≈50% of NSCLC cases, 61 Data are currently inadequate to indicate whether RT in patients with EGFR mutations is beneficial. Given the possible safety concerns raised in the RTOG study, concurrent TKI therapy is not routinely recommended in patients receiving WBRT.

Targeted Therapy with ALK Tyrosine Kinase Inhibitors

Although NSCLC with ALK rearrangement comprises a small subset of all NSCLC patients (4%–8%), this is an important subpopulation with distinct epidemiology and biology. Patients with ALK rearrangement (ALK-positive disease) are younger and usually have no or light smoking history. ALK-positive tumors are sensitive to ALKTKIs, with excellent systemic disease control. Initial findings from clinical trials of patients with ALK-positive NSCLC treated with ALK TKIs have shown promising CNS responses (Table 3). Crizotinib was the first ALK inhibitor approved for treatment of patients with metastatic ALK-positive NSCLC. While this drug has demonstrated clinically meaningful disease control, the brain is the most common or only site for disease progression.59, 60 This observation can likely be attributed to subtherapeutic crizotinib concentrations in the brain (Table 2). Pooled analysis of a phase 3 randomized trial (PROFILE 1007) with a single-arm phase 2 trial (PROFILE 1005) reported a 12-week intracranial disease control rate with crizotinib of 56% among 109 patients with untreated asymptomatic BM compared with 62% in 166 patients with previously treated BM.61 In the small subset of patients with CNS target lesions at baseline, the confirmed intracranial response rate was 18% in patients who did not receive brain RT and 33% in patients with previously treated BM. Thus, CNS disease control may be achievable with crizotinib initially but is not durable.

Second-generation ALK TKIs ceritinib, alectinib, and brigatinib have shown efficacy in crizotinib-resistant patients.

Table 1. Prevalence of brain metastases by subtype of lung, breast, and skin cancers

| Primary Tumor Site/Type | Frequency/Prevalence of Brain Metastases |
|-------------------------|-----------------------------------------|
| **Lung**                |                                         |
| NSCLC                   | 40%–50% of all BM;1,3                   |
| Somatic EGFR mutant     | ≈50% of NSCLC cases145                  |
| ALK positive            | 44% of NSCLC BM cases (despite a genotype prevalence of only 10% in nonsquamous NSCLC)31 |
| SCLC                    | 35%−50% of NSCLC BM cases26,32,64       |
|                         | 40%−50% of SCLC cases (10% of cases at diagnosis)186 |
| **Breast**              |                                         |
| Triple negative         | 15%−25% of all BM;1,3                   |
| HER2 positive           | 25%−46% ofTNBC cases93,126              |
| Luminal                 | 38% of HER2-positive breast cancer cases187 |
|                         | 5% of luminal breast cancer cases128    |
| **Melanoma**            |                                         |
| BRFWT                   | 5%−20% of all BM;1,3                   |
| BRF mutant              | ≤50% of melanoma cases148,188,189; 55%–75% of melanoma cases based on autopsy report1,148,149 |
|                         | Similar frequency of BM as BRF-WT melanoma190 |

Abbreviations: ALK, anaplastic lymphoma kinase; BM, brain metastases; BRF, v-Raf murine sarcoma viral oncogene homolog B; EGFR, epidermal growth factor receptor; HER2, human epidermal growth factor receptor 2; NSCLC, non–small cell lung cancer; SCLC, small cell lung cancer; TNBC, triple-negative breast cancer; WT, wild-type.
including activity against BM, in part because of improved BBB penetration (Tables 2 and 3). Ceritinib was approved for treatment of patients with metastatic ALK-positive NSCLC whose disease progressed while taking crizotinib or who are intolerant to crizotinib. Ceritinib is selective for ALK at low concentrations in vitro and exhibits activity against crizotinib-resistant tumors in ALK-positive NSCLC xenograft models. In a phase 1 trial of patients with ALK-positive advanced solid tumors (ASCEND-1), approximately half had BM at baseline, and single-agent ceritinib produced an objective response rate of 59% with responses observed in both crizotinib-pretreated and crizotinib-naive patients. Median PFS was 6.9 months in crizotinib-pretreated patients and 10.4 months in crizotinib-naive patients. In a 1-year follow-up, objective response rates were 56.4% (92/163) and 72% (80/83), respectively, with median duration of response of 8.3 and 170 months, respectively. Half of patients had BM, and the intracranial disease control rate was 65.3% (median time to intracranial response, 6.1 wk) in crizotinib-naive patients. An ongoing phase 2 study (NCT02336451) is specifically looking at the activity of ceritinib as first-line therapy in crizotinib-treated and crizotinib-naive patients with untreated, asymptomatic and measurable BM and leptomeningeal disease.

Results from dose-finding phase 1 and phase 2 studies indicate that alectinib has promising antitumor activity in patients with ALK-rearranged NSCLC after progression on crizotinib, including those with CNS metastases (Table 3). Intracranial response rates >60% have been reported with alectinib. Based on these data, alectinib was recently approved for treatment of patients with ALK-rearranged NSCLC who had progressed post-crizotinib. In recent phase 2 studies of alectinib in crizotinib-refractory, ALK-rearranged NSCLC, 51%–61% of patients had CNS metastases. Among patients with BM at baseline, the disease control rate was 83%, with a duration of response of 10.3 months. Alectinib is also being investigated specifically in patients with BM in several studies (NCT02075840, NCT02521051, and NCT02604342).

Brigatinib is another second-generation ALK inhibitor. In a phase 1 study of 79 patients with ALK-positive NSCLC, the response rate and disease control rate were 53% and 87%, respectively, in the 15 patients with measurable BM CNS disease. Lorlatinib (PF-06463922) has demonstrated clinical activity in patients with ALK-rearranged and ROS proto-oncogene 1, receptor tyrosine kinase (ROS1)-rearranged NSCLC with promising CNS efficacy.

Recent studies have demonstrated a survival benefit with the combination of TKI and RT in patients with BM from ALK-rearranged NSCLC. In a retrospective, multi-institution study examining OS and intracranial PFS in 90 patients, treatment with SRS or WBRT and TKIs prolonged survival.

Other potential molecular drivers and signaling transduction pathways—such as ROS1, RET proto-oncogene (RET), mesenchymal-epithelial transition factor receptor tyrosine kinase gene (MET), v-Raf murine sarcoma viral oncogene homolog B (BRAF), and tyrosine kinase receptor B (TRKB)—are being explored in early-phase clinical trials as therapeutic targets in NSCLC and other cancers. The ability of these agents to penetrate the CNS and elicit intracranial responses will be a major factor in developing these novel targeted therapies and improving the survival of patients with NSCLC.

Immunotherapy

Immune checkpoint inhibitors, particularly those targeting the programmed death 1 (PD-1) pathway, result in
Table 2. Physicochemical and pharmacokinetic properties of new targeted therapies that may be useful for treatment of brain metastases in non–small cell lung cancer, breast cancer, and melanoma

| Therapeutic Agent | MW, Da | Log P | BCRP and P-gp Substrate | Median Inhibitory Concentration, ng/ml | CSF Concentration in Patients with BM, ng/ml | CSF Penetration Rate in Patients with BM, % | Drug Efflux Transporters Restricted CNS Penetration, BCRP/P-gp | Clinical Development Status |
|------------------|--------|------|-------------------------|----------------------------------------|------------------------------------------|----------------------------------|---------------------------------|-----------------------------|
| Erlotinib        | 429.90 | 2.7  | Yes (EGFR-WT NSCLC)     | 7.9                                    | 24–54 (N = 25)                          | 2.8–5.1                          | Yes                            | FDA approved for locally advanced or metastatic EGFR-mutant NSCLC and locally advanced, unresectable or metastatic pancreatic cancer, in combination with gemcitabine |
| Gefitinib        | 446.9  | 3.2  | Yes (EGFR-WT NSCLC)     | 0.13                                   | 3.7–6.2 (N = 30)                       | 1.1–1.4                          | Yes                            | FDA approved for locally advanced or metastatic EGFR-mutant NSCLC |
| Afatinib         | 485.9  | 3.7  | Yes (EGFR-WT NSCLC)     | 0.5                                    | 0.5 (N = 1)                            | <1200                            | Unknown                        | FDA approved for metastatic EGFR-mutant NSCLC |
| Crizotinib       | 450.3  | 1.8  | Yes (EML4-ALK E13;A20 translocation; NCI-H3122; 48 [H228]) | 108                                   | 0.62 (N = 1)                           | 0.26                            | Yes                            | FDA approved for locally advanced or metastatic ALK-positive NSCLC |
| Ceritinib        | 558.1  | 5.0  | Unknown                 | Unknown (Ba/F3 NPM-ALK WT)             | 11                                      | Unknown                         | Yes                            | FDA approved for patients with ALK-positive NSCLC who have progressed on or are intolerant to crizotinib |
| Alectinib        | 482.6  | 5.5  | No (ALK cell-free assay) | 0.92                                   | 1.3                                    | 86                              | No                             | FDA breakthrough therapy designation for patients with ALK-positive NSCLC who have progressed on crizotinib |
| Nivolumab        | 146000 | N/A  | N/A                     | N/A                                    | Not expected to cross intact BBB       | Mechanism of action is in the periphery on T cells, which then cross the BBB | FDA approved for: (1) advanced squamous NSCLC after platinum-based chemotherapy; and (2) unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF-V600-mutation positive, a BRAF inhibitor |
| Trastuzumab      | 145000 | N/A  | N/A                     | N/A                                    | Not expected to cross intact BBB       |                                   | FDA approved for HER2-overexpressing breast cancer, and HER2-overexpressing metastatic gastric or gastroesophageal junction adenocarcinoma |
| Lapatinib        | 580.5  | 5.1  | Yes (EGFR and HER2)     | 1.3–4.5 (N = 2)                        | 0.9–1.3                                | Yes                             | FDA approved as part of combination treatment for advanced or metastatic (with an anthracycline, a taxane, and trastuzumab) and postmenopausal (with letrozole) HER2-overexpressing breast cancer |
| Therapeutic Agent | MW, Da | Log P | BCRP and P-gp | Median Inhibitory Concentration, ng/ml | CSF Concentration in Patients with BM, ng/ml | CSF Penetration Rate in Patients with BM, % | Drug Efflux Transporters Restricted CNS Penetration, BCRP/P-gp | Clinical Development Status |
|-------------------|--------|-------|---------------|----------------------------------------|---------------------------------------------|---------------------------------------------|-----------------------------------------------|-------------------------------|
| Vemurafenib       | 489.9  | 5.1   | Yes\(^{[6,7,10]}\) | Yes\(^{[10]}\)  | 470 (N = 6)\(^{[11]}\) | 0.98\(^{[12]}\) | Yes\(^{[13]}\)  | FDA approved for unresectable or metastatic melanoma with BRAF-V600E mutation |
| Dabrafenib        | 615.7  | 5.4   | Yes\(^{[11,13]}\) | Unknown | Unknown | Unknown | Yes\(^{[11]}\) | FDA approved for unresectable or metastatic melanoma with BRAF-V600E mutation and in combination with trametinib for BRAF-V600E and BRAF-V600K mutations |
| Ipilimumab        | 148000 | N/A   | N/A | N/A | <148 (CTLA-4)\(^{[14]}\) | Not expected to cross intact BBB. Mechanism of action is in the periphery on T cells, which then cross the BBB | | FDA approved for unresectable or metastatic melanoma |
| Pembrolizumab     | 149000 | N/A   | N/A | N/A | Not expected to cross intact BBB. Mechanism of action is in the periphery on T cells, which then cross the BBB | | | FDA approved for unresectable or metastatic melanoma and disease progression following ipilimumab and, if BRAF-V600 mutation positive, a BRAF inhibitor |

**Abbreviations:** ALK, anaplastic lymphoma kinase; BBB, blood-brain barrier; BCRP, breast cancer resistance protein; BM, brain metastases; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CNS, central nervous system; CSF, cerebrospinal fluid; CTLA-4, cytotoxic T-lymphocyte antigen; EGF, epidermal growth factor receptor; EML4, echinoderm microtubule associated protein like 4; FDA, U.S. Food and Drug Administration; HER2, human epidermal growth factor receptor 2; MW, molecular weight; N/A, not applicable; NCI, National Cancer Institute; NPM, nucleophosmin; NSCLC, non–small cell lung cancer; P-gp, P-glycoprotein; WT, wild type.

\(^{a}\) Obtained from the PubChem Compound Database (http://www.ncbi.nlm.nih.gov/pccompound).

\(^{b}\) Obtained from the Drugbank database (http://www.drugbank.ca/) and Chemsper database (http://www.chemspider.com).

\(^{c}\) Assessed using human blood and CSF samples.

\(^{d}\) Based on nonclinical studies using mouse models.

\(^{e}\) Alectinib was not transported by P-gp in cell transport assay, suggesting it is a poor or non-P-gp substrate.
### Table 3. Efficacy of whole brain radiation therapy and targeted therapies for brain metastases from non–small cell lung cancer, stratified by driver mutation status

| Publication and Study Design | No. and Type of Patients | Any Prior Therapy for BM | Targeted Therapy Dosage Regimen | Intracranial ORR, % (CR + PR) | Intracranial Disease Control, % (CR + PR + SD) | Median Time to CNS Progression, mo | PFS, mo | OS, Incidence or Median Duration |
|-----------------------------|--------------------------|--------------------------|--------------------------------|------------------------------|-----------------------------------------------|----------------------------------|--------|-----------------------------|
| **Studies of unselected patients with NSCLC** |
| Ceresoli et al., prospective, noncomparative | 41 consecutive (80% platinum pretreated) | WBRT, 44% | Gefitinib 250mg/d | 10 | 27 | NR | 3 | 27% at 11 mo |
| Wu et al., phase 2 | 40 chemotherapy pretreated | Gefitinib 250mg/d | 32 [0 + 32] | 77 | NR | 9 | 15 mo |
| Kim et al., prospective, noncomparative | 23 Korean never-smokers; chemotherapy-naive | No | Gefitinib 250mg/d or Erlotinib 150mg/d | 70 [0 + 70] | 74 | NR | 7.1 | 18.8 mo |
| Pesce et al., multicenter, randomized phase 2 | 59 | Only prior chemotherapy allowed | WBRT + temozolomide 75mg/m² x 21/28 d (N = 43) | NR | NR | 1.8 | 1.8 | 4.9 mo |
| Sperduto et al., multicenter, randomized phase 3 | 125 with 1–3 BM | Prior brain resection allowed | WBRT + SRS (N = 44) | NR | NR | 8.1 | NR | 13.4 mo |
| **Studies in EGFR-mutant NSCLC** |
| Gow et al., retrospective | 63 Taiwanese with BM from adenocarcinomas (73% mutant) | No | WBRT | All, 46*<br> EGFRWT, 24*<br> EGFR mutant, 54**<br> All, 67*<br> EGFR mutant, 84* | NR | NR | NR | 14.7 mo |
| Eichler et al., retrospective | 93 (44% mutant) | 83% WBRT (alone, 53%; + craniotomy, 22%; + SRS, 8%; 5% erlotinib) | Treatment with TKI after BM diagnosis (EGFRWT, 19%; EGFR mutant, 78%) | NR | NR | EGFRWT, 8.4 | NR | EGFRWT, 7.6 mo |
| Lee et al., retrospective | 43 (70% mutant) | No | WBRT (31% of EGFR-WT 50% of EGFR-mutant patients also received a TKI) | All, 70 (12 + 58) EGFRWT, 46 EGFR mutant, 80* | 84 | 18 | 12 | 11 mo |

* indicates statistical significance.
| Publication and Study Design | No. and Type of Patients | Any Prior Therapy for BM | Targeted Therapy Dosage Regimen | Intracranial ORR, % (CR + PR) | Intracranial Disease Control, % (CR + PR + SD) | Median Time to CNS Progression, mo | PFS, mo | OS, Incidence or Median Duration |
|-----------------------------|--------------------------|--------------------------|-------------------------------|-----------------------------|---------------------------------|---------------------------------|------|-----------------------------|
| Porta et al.,\(^38\) retrospective | 69 (25% mutant) | 80% WBRT | Erlotinib 150 mg/d\(^b\) | All, 26 (15 + 11) | EGF R mutant, 82 (47 + 35)\(^***\) | NR | 2.9 | 11.7 | NR | 4.3 mo | 12.9 mo |
| Park et al.,\(^39\) open-label, single-center phase 2 | 28 Korean with mutant EGF R | No | Gefitinib 250 mg/d (N = 22) or erlotinib 150 mg/d (N = 6) | NR | 93 | 6.6 | NR | All, 15.9 mo |
| Wu et al.,\(^40\) open-label, multicenter phase 2 | 48 Chinese with asymptomatic BM; chemotherapy pretreated (17% mutant EGF R) | No | Erlotinib 150 mg/d | All, 58 (4 + 54) EGF RWT, 33 (0 + 33) EGF R mutant, 75 (12 + 62) | NR | All, 10.1 EGF RWT, 4.4\(^d\) EGF R mutant, 15.2\(^e\)** | NR | All, 18.9 EGF RWT, 18.4 mo EGF R mutant, 37.5 mo |

**Studies in ALK-positive NSCLC**

| Publication | No. and Type of Patients | Any Prior Therapy for BM | Targeted Therapy Dosage Regimen | Intracranial ORR, % (CR + PR) | Intracranial Disease Control, % (CR + PR + SD) | Median Time to CNS Progression, mo | PFS, mo | OS, Incidence or Median Duration |
|-------------|--------------------------|--------------------------|-------------------------------|-----------------------------|---------------------------------|---------------------------------|------|-----------------------------|
| Costa et al.,\(^61\) retrospective | 275 asymptomatic with BM | 60% WBRT | Crizotinib 250 mg BID | 33\(^a\) | 62\(^f\) | 13.2 | 6.0 | 74% at 6 mo |
| Shaw et al.,\(^215\) phase 1 | 124 (74 with BM) | 79% ALK inhibitor | Ceritinib 750 mg/d | All, 35 Pretreated, 29 Treatment-naive, 60 | NR | NR | 8.3 | NR |
| Mok et al.,\(^216\) open-label multicenter phase 2 | 20\(^g\) | Chemotherapy and crizotinib | Ceritinib 750 mg/d | NR | 80 | NR | 5.4 | NR |
| Felip et al.,\(^217\) open-label multicenter phase 2 | 10 ALK inhibitor naïve\(^a\) | Prior chemotherapy allowed | Ceritinib 750 mg/d | NR | 80 | NR | NR | NR |
| Gadgeel et al.,\(^67\) open-label multicenter phase 1/2 | 21 with resistance or intolerance to crizotinib | 81% WBRT, 95% chemotherapy | Alectinib 300–900 mg BID | 52 (29 + 24) | 62 | NR | NR | NR |
| Gandhi et al.,\(^68\) open-label multicenter phase 2 | 16 with BM after crizotinib\(^g\) | Prior chemotherapy allowed | Alectinib 600 mg BID | 69 (13 + 56) | 100 | NR | NR | NR |
| Ou et al.,\(^69\) open-label multicenter phase 2 | 34 with BM after crizotinib\(^g\) | Prior chemotherapy allowed | Alectinib 600 mg BID | 56 (15 + 41) | NR | NR | NR | NR |
| Camidge et al.,\(^218\) open-label multicenter phase 1/2 | 12 | All other therapies allowed | Brigatinib 30–300 mg/d | 50 | NR | 22 | NR | NR |
impressive disease control in a subset of patients with NSCLC. Tumors evade the immune system using multiple mechanisms including the expression of PD-1 ligands (PD-L1 or PD-L2) by cells in the tumor microenvironment; binding of PD-L1 or PD-L2 to PD-1 receptors leads to inhibition of cytotoxic T cells. Pharmacologic inhibition of the PD-1 receptor/ligand interaction reverses such immune evasion and restores T-cell immunity against the tumor.77,78 Notably, PD-1 inhibitors lead to systemic activation of T cells, which can cross the BBB.79,80 Two monoclonal antibodies to PD-1, nivolumab and pembrolizumab, are approved for the treatment of NSCLC. Although the objective response rate is generally low with these agents, responses are impressively durable, and treatment leads to a meaningful survival improvement in responders while preserving quality of life.

Phase 3 studies confirming the efficacy of nivolumab as second-line therapy for NSCLC included patients with treated stable BM27,28; there was no indication of increased neurological complications or toxicities in these patients. A large phase 1 study has demonstrated the efficacy of pembrolizumab in the treatment of advanced NSCLC (objective response rate, 19%; median duration of response, 12.5 mo); however, only 10% of patients included in the study had BM.29 Preliminary results from an ongoing phase 2 trial of pembrolizumab showed an intracranial response rate of 45% in 11 patients with untreated BM; there were no serious neurologic complications.30 These early data show that immune checkpoint inhibitors may be an effective treatment for patients with BM, although whether the responses are durable remains to be determined. There are ongoing trials specifically looking at responses of BM from NSCLC and/or melanoma to nivolumab (NCT02621515, NCT02374242, and NCT02320058) and pembrolizumab (NCT02085070).31

Chemotherapy

In patients who are refractory to targeted TKI treatments or refractory to or not candidates for immunotherapy, cytotoxic therapy remains an option for suitable patients with NSCLC and will continue to play a role in providing modest systemic responses and improving survival. Intracranial responses with cytotoxic chemotherapy usually correlate with systemic responses in patients with NSCLC. Intracranial responses with cytotoxic chemotherapy usually correlate with systemic responses in patients with NSCLC. Intracranial response rates as high as 68% have been reported with chemotherapy in asymptomatic patients81; however, PFS is usually limited to several months, and OS ranges from 5 to 16 months (Table 4). The best intracranial outcomes were achieved using regimens containing cisplatin and pemetrexed82,83 or bevacizumab, carboplatin, and paclitaxel.81

Brain Metastases from Breast Cancer

Autopsy reports indicate that the incidence of BM in women with metastatic breast cancer is as high as 30%.84-86 There is also evidence of an increasing incidence of BM from breast cancer.8 Notably, according to the GPA, prognostic
Table 4. Efficacy of cytotoxic chemotherapies for brain metastases from non–small cell lung cancer

| Publication and Study Design | No. and Type of Patients | Any Prior Local Therapy for BM | Dosage Regimen | ORR, % (CR+PR) | Intracranial ORR, % (CR + PR) | Intracranial Disease Control, % (CR + PR + SD) | Median Overall PFS, mo | Median Time to CNS Progression, mo | Median OS, mo |
|-----------------------------|--------------------------|--------------------------------|---------------|---------------|-------------------------------|-----------------------------------------------|-----------------------|-------------------------------|----------------|
| Robinet et al., phase 3     | 176 inoperable single BM | No                             | Cisplatin 100mg/m² on d 1 and vinorelbine 30mg/m² on d 1, 8, 15, 22 Q4W + WBRT 30 Gy/10 fx/12 on progression (arm A) or on d 1 (arm B) | Arm A: 21 | Arm A, 27 (1+26) | NR                             | Arm A, 4 | NR                            | Arm A, 6 |
| Barlesi et al., phase 2     | 43 asymptomatic inoperable BM | No                             | Cisplatin 75mg/m² + pemetrexed 500mg/m² Q3W for 4 cycles a | 35 | 42 (2+40) | 84 | 4.0 | NR | 7.4 |
| Galetta et al., phase 2     | 25 asymptomatic inoperable BM | No                             | 2 cycles of fotemustine 80 mg/m² d 1, 8 and cisplatin 80mg/m² d 1, Q3W | 12 (0+12) | NR | 60 | 2.6 | NR | 4.7 |
| Dinglin et al., phase 2     | 41 newly diagnosed inoperable BM | No                             | Cisplatin 75mg/m² + pemetrexed 500mg/m² Q3W for 6 cycles + WBRT 30 Gy/10 fx/12 d on d 1–12 of cycle 1 | 37 (0+37) | 68 (2+66) | 975 | 8.9 | 10.6 | 12.6 |
| Besse et al., phase 2       | 67 asymptomatic BM        | No                             | Bevacizumab 15 mg/kg + carboplatin AUC x 6 + paclitaxel 200mg/m² Q3W | 63 | 61 | NR | 6.7 | NR | 16.0 |
| Brosnan et al., retrospective | 8 progressive BM          | WBRT + SRS                     | Bevacizumab + irinotecan | NR | >50% | NR | 4.0 | NR | 5.2 |

**Abbreviations:** AUC, area under the concentration-time curve; BM, brain metastases; CNS, central nervous system; CR, complete response; d, day; NR, not reported; NSCLC, non–small cell lung cancer; mo, month; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; Q4W, every 4 weeks; SD, stable disease; SRS, stereotactic radiosurgery; WBRT, whole-brain radiotherapy.  
*a* Responding patients were eligible for 2 additional cycles.
index patients with BM from breast cancer have the longest median OS (13.8 mo). Several oncogenes have been identified as drivers of breast cancer (Fig. 3), and the propensity for BM from breast cancer is dependent on tumor subtype, with the highest frequency of BM observed in patients with triple-negative breast cancer (TNBC), followed by human epidermal growth factor receptor 2 (HER2)-positive and luminal breast cancers (Table 1).

Patients with HER2-positive metastatic breast cancer are 2–4 times more likely to develop BM than patients with HER2-negative disease. The standard of care for this common complication of breast cancer includes WBRT, SRS, and surgery, which yield a median OS of 1–2 years in patients with HER2-positive breast cancer and ≤7 months in patients with TNBC.

Targeted Therapies

The failure of trastuzumab to prevent CNS relapse among patients with HER2-positive breast cancer can be ascribed to a lack of BBB penetration due to its large size. While fewer BM tend to occur in treatment arms containing small molecules (ie, lapatinib and/or capecitabine) than in those containing large biologics such as trastuzumab, pertuzumab, or ado-trastuzumab emtansine (T-DM1), OS in patients with BM is substantially improved in patients randomized to better-performing treatment arms.

Finally, neratinib, an irreversible HER2-targeting small molecule TKI, plus paclitaxel may be more effective than trastuzumab plus paclitaxel in reducing CNS progression from HER2-positive metastatic breast cancer.

Therapies for Brain Metastases from HER2-positive Breast Cancer

Overview

Until recently, development of targeted treatments in patients with BM and breast cancer was a low priority as BM presents at an advanced stage with little appreciable effect on OS. Currently, the only nonendocrine therapeutic target in breast cancer is HER2, which is overexpressed in 25%–30% of patients. The development of HER2-targeting therapies has been associated with an improvement in OS. Consequently, controlling or preventing BM in patients with HER2-positive breast cancer has increasingly become an important treatment consideration.

In patients with HER2-positive metastatic breast cancer, the recommended first-line systemic treatment is a combination of pertuzumab, trastuzumab, and taxane. Patients with active BM from HER2-positive breast cancer were excluded from participation in the pivotal clinical trials supporting this combination, and treatment regimens containing trastuzumab or lapatinib failed to prevent CNS relapse (MA.31 trial: lapatinib arm 18%, trastuzumab arm 24%; CLEOPATRA: 13% in both treatment arms; CEREDEL: lapatinib arm 3%, trastuzumab arm 5%). In a phase 3 randomized study of capecitabine plus lapatinib versus capecitabine alone for advanced-stage trastuzumab-refractory breast cancer, fewer patients in the combination arm had symptomatic CNS progression as part of the first progression event compared with those not receiving lapatinib.

There is evidence that treatment regimens containing capecitabine may afford greater protective efficacy against BM from HER2-positive breast cancer, and capecitabine alone is known to have activity within the CNS, even in the absence of concurrent HER2-directed therapy.

While fewer BM tend to occur in treatment arms containing small molecules (ie, lapatinib and/or capecitabine) than in those containing large biologics such as trastuzumab, pertuzumab, or ado-trastuzumab emtansine (T-DM1), OS in patients with BM is substantially improved in patients randomized to better-performing treatment arms.

Finally, neratinib, an irreversible HER2-targeting small molecule TKI, plus paclitaxel may be more effective than trastuzumab plus paclitaxel in reducing CNS progression from HER2-positive metastatic breast cancer.
Table 5. Efficacy of targeted therapies for brain metastases from HER2-amplified breast cancer

| Publication and Study Design | No. and Type of Patients | Any Prior Therapy for BM | Targeted Therapy Dosage Regimen | Intracranial ORR, % (CR + PR) | Intracranial Disease Control, % (CR + PR + SD) | Median Time to CNS Progression, mo | PFS, mo | OS, Incidence or Median Duration |
|-----------------------------|--------------------------|--------------------------|--------------------------------|-----------------------------|---------------------------------|--------------------------------|---------|---------------------------------|
| Bartsch et al.,<sup>109</sup> case-control retrospective | 17 | WBRT | Trastuzumab 8 mg/kg STAT then 6 mg/kg Q3W | NR | NR | 6 | NR | 7 mo |
| Park et al.,<sup>110</sup> retrospective | 78 with symptomatic BM | WBRT, SRS, intrathecal chemotherapy | Trastuzumab before BM 42 68 3.9 NR | Trastuzumab after BM 44 72 7.8 NR | No trastuzumab 2.9 | | |
| Church et al.,<sup>111</sup> retrospective | 26 chemotherapy pretreated | Neurosurgery, SRS, WBRT | Trastuzumab | NR | NR | NR | NR | HER2 amplified, 11.9 mo* |
| Krop et al.,<sup>104</sup> phase 3 subgroup analysis | 95 with BM after trastuzumab and a taxane | 69% WBRT and/or local treatment | T-DM1 (N = 45) | NR | NR | NR | 5.9 | 26.8 mo* |
| Lin et al.,<sup>112</sup> phase 2 | 39 with BM after trastuzumab | 95% WBRT or SRS or both | Lapatinib 750mg BID | 2.6 (0 + 2.6) 15.4<sup>a</sup> | NR | 3.0 |
| Lin et al.,<sup>113</sup> open-label, multicenter phase 3 | 242 with BM after trastuzumab 50 phase 2 completers | 95% WBRT; 26% SRS | Lapatinib 750mg BID | 6 (0 + 6)<sup>b</sup> 43 | 2.4 | 6.4 mo |
| Freedman et al.,<sup>115</sup> open-label, multicenter phase 2 | 40 with BM after CNS-directed therapy | 78% WBRT | Neratinib 240mg QD | 8 (0 + 8) | NR | 1.9 | 8.7 mo |
| Bartsch et al.,<sup>118</sup> retrospective | 43 with KPS >70 | Local therapy | Trastuzumab ± chemotherapy (N = 28) | NR | NR | NR | NR | 13 mo |
| Bachelot et al.,<sup>121</sup> open-label, multicenter phase 2 | 44 with untreated BM | No | Lapatinib 1250 mg/d + capecitabine (2 g/m<sup>2</sup> d −14) x 21 d | 66 (0 + 66) | NR | 5.5 | 5.5 | 170 |

Abbreviations: BID, twice daily; BM, brain metastases; CNS, central nervous system; CR, complete response; d, day; HER2, human epidermal growth factor receptor 2; KPS, Karnofsky Performance Score; mo, month; NR, not reported; NYR, not yet reached; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; Q3W, every 3 weeks; QD, once daily; SD, stable disease; SRS, stereotactic radiotherapy; STAT, loading dose; T-DM1, ado-trastuzumab emtansine; WBRT, whole brain radiotherapy.

<sup>a</sup>In both CNS and non-CNS sites.
<sup>b</sup>Compared with an ORR of 15% in the 130 patients with measurable extra-CNS disease at baseline.

<sup>*</sup>P < .01 vs comparator arm.
Combinational Therapies

There is also interest in a combination of trastuzumab and nanoparticle albumin-bound paclitaxel following intensive objective response rates and PFS as first-line treatment for metastatic breast cancer (excluding BM). Case-controlled data indicate that median OS was improved in patients with BM from HER2-positive breast cancer when lapatinib was added to trastuzumab (not yet reached) compared with trastuzumab alone (13 mo). The efficacy of lapatinib alone in the treatment of active BM from HER2-positive breast cancer was increased when coadministered with capecitabine (objective response rate, 38% with lapatinib plus capecitabine vs 0% with lapatinib plus topotecan). Furthermore, the addition of lapatinib to capecitabine significantly prolonged time to tumor progression relative to capecitabine alone (8.4 vs 4.4 mo) in patients with metastatic HER2-positive breast cancer, although progressive BM was an exclusion criterion. Subsequent findings from the phase 2 LANDSCAPE trial established primary systemic therapy with lapatinib plus capecitabine as an effective and safe alternative to WBRT in patients with asymptomatic to oligosymptomatic BM from HER2-positive breast cancer. The intracranial response rate was 66% in this selected population, thereby delaying the need for WBRT by 8.3 months. A prospective study showed significant uptake of both lapatinib and capecitabine into BM following surgical resection in patients with metastatic breast cancer.

Dual anti-HER2 therapy with trastuzumab and lapatinib plus capecitabine was an effective and well-tolerated regimen in patients with metastatic HER2-positive breast cancer. One case report describes how trastuzumab and lapatinib plus capecitabine as second-line therapy after T-DM1 resulted in partial remission of BM without systemic disease progression and a >14-month delay in time to WBRT.

Finally, in a case series, ONT-380, a HER2-targeting cova- lently binding TKI, demonstrated promising activity against BM from HER2-positive breast cancer in combination with other systemic agents.

Therapies for Brain Metastases from Other Breast Cancer Subtypes

Targeted Therapies and Hormonal Manipulation

Up to 40% of patients with TNBC develop symptomatic BM during the course of their disease, yet no targeted therapies for this disease subtype have been developed. Notably, the high expression of PD-L1 in TNBC suggests that this pathway is a potential therapeutic target. In preliminary results of a phase 1 study (KEYNOTE 012) of pembrolizumab, patients with TNBC (13% with BM) had an overall response rate of 19%. Furthermore, several ongoing clinical trials are investigating pembrolizumab in TNBC (NCT02447003, NCT02555657, NCT02622074, NCT02513472, and NCT02648477).

About 5% of patients with metastatic luminal-type, estrogen-receptor–overexpressing breast cancer develop BM during their course of disease. Of note, estrogen-receptor expression changes from initial overexpression in the primary tumor to absence of expression in the corresponding BM in up to 50% of cases. Moreover, in cases where the estrogen receptor continues to be expressed, the estrogen receptor 1 gene (ESR1) often contains mutations that result in a constitutively active protein. Concentrations of the estrogen receptor antagonist tamoxifen and its metabolites have been shown to be up to 46-fold higher in brain tissue and BM than in serum. Furthermore, case reports of patients with BM from breast cancer have demonstrated prolonged survival and prolonged remissions with tamoxifen endocrine therapy, the aromatase inhibitor letrozole, and the progesterin megestrol acetate. With more clinically approved drugs for estrogen-receptor–expressing breast cancer, including the mechanistic target of rapamycin (mTOR) inhibitor everolimus, it will be of interest to see if a further extension of survival is possible for TNBC BM. Despite an ability to cross the BBB, palbociclib, an inhibitor of cyclin-dependent kinase (CDK)4/6 recently approved for first- and subsequent-line management of hormone-receptor–positive metastatic breast cancer, is unlikely to be effective against BM from breast cancer as it is a substrate for CNS drug efflux pumps.

Chemotherapy

When treating BM from breast cancer with cytotoxic chemotherapy, agents that exert antitumor activity against breast cancer in the extraneural compartment are selected as opposed to agents with extensive penetration of the BBB but limited systemic activity (eg, temozolomide). In patients naive to cyclophosphamide and anthracyclines, FEC (5-FU, epirubicin, cyclophosphamide) and CMF (cyclophosphamide, methotrexate, 5-FU) have purported activity in patients with BM. Of the few cytotoxic chemotherapeutic agents that can penetrate the BBB when disrupted by BM or radiation, cisplatin demonstrated clinical activity in patients with BM from breast cancer, particularly TNBC, as a single agent and in combination with other chemotherapies or with vinorelbine plus WBRT. Phase 2 trials have also been completed evaluating capecitabine monotherapy in patients with CNS progression after WBRT alone or with SRS and no prior systemic therapy for BM (NCT01077726, NCT00977379, and NCT00570908).

The novel cytotoxic agent sagozolone, a microtubule stabilizer that penetrates the BBB and is not a substrate for CNS efflux transporters, has been evaluated in a single-arm, phase 2 study of 15 breast cancer patients with BM. A CNS partial response was seen in 13% of patients, with a median PFS and OS of 1.4 and 5.3 months, respectively. Additionally, a peptide-facilitated, brain-penetrating formulation of paclitaxel (GRN1005) was well tolerated and decreased tumor size in heavily pretreated patients with advanced solid tumors, including those who had BM and/or failed prior taxane therapy.

Brain Metastases from Melanoma

An estimated 50% of patients with stage IV melanoma develop BM, but the prevalence may be as high as 75% based on autopsy reports. According to the GPA for
BM, patients with BM from melanoma have a median OS of 6.74 months.\textsuperscript{16} Patients with multiple BM and extensive extracranial disease have extremely poor survival outcomes (as short as 1–2 mo in neurologically symptomatic patients).\textsuperscript{150,151} The prognosis may be somewhat better for patients with brain involvement at initial diagnosis of stage IV melanoma than for those who develop BM later.\textsuperscript{152} Some patients with solitary BM without known extracranial disease may survive for several years after local treatment.\textsuperscript{152,153}

Melanoma is generally not considered as sensitive to RT or traditional cytotoxic chemotherapy as many other primary malignancies, and these treatment shortcomings are accentuated when a patient develops BM. While surgery and RT may lead to prolonged survival and symptom palliation in patients with oligometastatic CNS involvement, these therapies do not protect against development of new BM.\textsuperscript{154} Systemic therapy, although underinvestigated in melanoma patients with CNS involvement, represents a more viable treatment approach for what is essentially a systemic disease with subclinical metastases. Temozolomide and fotemustine were considered promising treatments for BM because of their CNS penetration; however, response rates with these agents were poor, and responses were transient. Fortunately, recent advances in systemic therapy for melanoma, both in molecularly targeted therapy and immunotherapy, render new hope for effective use of systemic agents for BM.

**Targeted Therapy with BRAF and/or MEK Inhibitors**

Recent discoveries have identified numerous driver genetic mutations in melanoma, particularly in BRAF and neuroblastoma RAS viral (v-Ras) oncogene homolog (NRAS; Fig. 4). Approximately 40%–60% of melanoma patients harbor a BRAF driver mutation, which results in the substitution of valine at codon 600 of the BRAF serine-threonine kinase (BRAF V600). The small molecule BRAF inhibitors dabrafenib and vemurafenib target the RAF/MEK/ERK (MAPK) pathway,\textsuperscript{155,156} and are associated with high response rates and improved survival in metastatic melanoma patients with BRAF V600-mutant tumors.\textsuperscript{157,158} The efficacy is improved further when BRAF inhibitors are used in combination with MEK inhibitor therapy to counter reactivation of the MAPK pathway.\textsuperscript{159–161} BRAF inhibitors are associated with quick-onset regressions in the vast majority of patients and represent a rational option for control and palliation of BM from melanoma.

BRAF inhibitors have been associated with intracranial responses despite limited intracranial bioavailability (Table 2).\textsuperscript{162} Dabrafenib therapy led to regression of BM in a phase 1 trial of patients with untreated BM from BRAF V600-mutant melanoma.\textsuperscript{163} In a phase 2 trial of patients with BRAF V600E-mutant melanoma, dabrafenib resulted in comparable intracranial and overall response rates (39% and 38%, respectively) in those with previously untreated BM and similar response rates (31% and 31%, respectively) in those with progressive BM despite prior treatment, indicating that the central and peripheral activity of this agent is concordant (Table 6).\textsuperscript{164} Duration of response in this study ranged from 20 to 28 months. Similarly, in an open-label trial of patients with BRAF V600-mutant melanoma and symptomatic BM, vemurafenib demonstrated antitumor activity at both intracranial and extracranial sites, with a duration of response in the brain of 4.4 months (Table 6).\textsuperscript{165} MEK inhibition with MEK162 was also promising in a phase 2 study that included patients with treated and stable BM harboring NRAS or BRAF mutations.\textsuperscript{166} Dual BRAF and MEK inhibition (eg, with dabrafenib plus trametinib or vemurafenib plus cobimetinib) is now established as the standard of care for appropriately selected patients with advanced melanoma and tumors that harbor a BRAF V600 mutation, although the efficacy in patients with BM has not yet been determined.\textsuperscript{159,161}

**Immunotherapy**

Another major drug development in melanoma has been the approval of immune checkpoint inhibitors targeting the PD-1 and cytotoxic T-lymphocyte–associated antigen 4 (CTLA-4) pathways. The anti-CTLA-4 monoclonal antibody ipilimumab was approved after demonstration of improved OS in previously treated patients with metastatic melanoma.\textsuperscript{167} Ipilimumab was investigated in a phase 2 trial of patients with advanced melanoma and BM.\textsuperscript{168} In the cohort of patients with neurologically asymptomatic disease who were not receiving corticosteroid treatment at study entry (N = 51), ipilimumab elicited a CNS response of 16% and CNS disease control rate of 24%, with intracranial responses generally concordant with extracranial responses. The 2-year survival rate in this cohort was 26%, suggesting the possibility of long-term survival in a sizable proportion of patients with an otherwise poor prognosis.

Nivolumab and pembrolizumab have also been approved for treatment of advanced melanoma.\textsuperscript{169,170} Nivolumab was associated with significant improvements in OS
### Table 6. Efficacy of targeted therapies for brain metastases from metastatic melanoma

| Publication and Study Design | No. and Type of Patients | Any Prior Local Therapy for BM | Targeted Therapy Dosage Regimen | ORR, % (CR + PR) | Intracranial ORR, % (CR + PR) | Disease Control, % (CR + PR + SD) | Intracranial Disease Control, % (CR + PR + SD) | Median Duration of Intracranial Response, mo | Median Overall PFS, mo | Median OS, mo |
|-----------------------------|--------------------------|--------------------------------|---------------------------------|-----------------|-----------------------------|--------------------------------|----------------------------------------|------------------------------------------|-------------------------|------------------|
| Long et al., 164 multi-center phase 2 | BRAF-V600E mutant BM (N = 139) | 47% | Dabrafenib 150mg BID | 378 | 39.2 | 79.7 | 81.1 | 4.6 | 3.7 | 7.6 |
| Dummer et al., 165 pilot study | BRAF-V600K mutant BM (n = 33) | 54% | 0 | 278 | 22.2 | 50.0 | 50.0 | 3.8 | 3.7 | 5.0 |
| Margolin et al., 168 multicenter phase 2 | BRAF-V600 mutation with symptomatic BM (N = 24) | Yes | Vemurafenib 960 mg BID | 42 (0 + 42) | 16 (0 + 16)\(^a\) | 80 | 84\(^a\) | 4.4\(^b\) | 3.9 | 5.3 |
| | Asymptomatic BM (N = 51) | 41% | Ipilimumab 10mg/kg | 10 (0 + 10) | 16 (0 + 16) | 18 | 24 | NR | 1.4\(^c\) | 7.0 |
| | Symptomatic BM (N = 21) | 48% | Ipilimumab 10mg/kg + corticosteroids | 5 (0 + 5) | 5 (5+0) | 5 | 10 | NR | 1.2\(^d\) | 3.7 |

**Abbreviations:** BID, twice daily; BM, brain metastases; BRAF, v-Raf murine sarcoma viral oncogene homolog B; CR, complete response; mo, month; NR, not reported; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; PR, partial response; SD, stable disease.

\(^a\)Among 19 patients with measurable intracranial disease at baseline.

\(^b\)Compared with a median of 1.5 months for disease progression in the brain.

\(^c\)Compared with a median of 1.2 months for disease progression in the brain.
and PFS relative to dacarbazine in previously untreated patients without a BRAF mutation.\textsuperscript{171} Pembrolizumab was associated with prolonged PFS and OS and a more favorable toxicity profile than ipilimumab in patients with advanced melanoma who had not received previous therapy with immune checkpoint inhibitors.\textsuperscript{172} Additionally, pembrolizumab resulted in a high rate of sustained tumor regression among patients with advanced melanoma, including those with disease progression despite receiving ipilimumab.\textsuperscript{173}

To date, there are no published data on the safety and efficacy of pembrolizumab or nivolumab for BM from melanoma because patients with active BM were excluded from entering these studies.\textsuperscript{171–173} However, several trials of nivolumab and pembrolizumab are specifically investigating response in BM from melanoma (NCT02621515, NCT02374242, NCT02320058, and NCT02085070).\textsuperscript{166} An interim analysis of the ongoing clinical trial of pembrolizumab (NCT02085070) reported durable partial responses in melanoma patients with untreated BM.\textsuperscript{174} Another ongoing trial is investigating the safety and efficacy of the combination of nivolumab plus ipilimumab in this setting (NCT02320058).\textsuperscript{166}

**Chemotherapy**

Cytotoxic therapies have had only modest activity against melanoma in general and therefore have limited utility in the treatment of BM from melanoma. Dacarbazine, the long-standing standard of care for metastatic melanoma, has not reliably demonstrated response in CNS metastasis across numerous trials.\textsuperscript{175,176} Although the oral dacarbazine analog temozolomide has improved capacity to cross the BBB, most studies report response rates of <10% in patients with BM.\textsuperscript{176,177} Fotemustine, a nitrosourea that crosses the BBB, showed promise in early trials that included patients with BM, but intracranial response rates were low (6%) in later trials.\textsuperscript{178,179}

**Local and Systemic Combinatorial Approaches**

The synergistic potential of RT in facilitating an immune response from immune checkpoint blockade is under evaluation. In a single-institution study of patients with BM from melanoma, univariate analysis revealed that SRS before or during treatment with ipilimumab was associated with higher rates of OS at 1 year than SRS after ipilimumab (65% vs 56% vs 40%) and fewer instances of regional brain recurrences at 1 year (64% or 69% vs 92%).\textsuperscript{180} There was a trend toward improved local control in those who received SRS concomitantly with ipilimumab (1-y local recurrence, 0%) compared with those who received SRS before (13%) or after (11%) ipilimumab.

Outcomes in patients with BM from BRAF V600E-mutant melanoma when combining SRS or WBRT prior to or concomitantly with vemurafenib were also positive in a retrospective analysis.\textsuperscript{181} Most evaluable patients had an improvement in neurological symptoms (7/11; 64%) and a radiographic response of index lesions (36/48; 75%), of which 23 (48%) were complete responses and 13 (27%) were partial responses. The CNS local control rate, freedom from new BM, and OS at 6 months were 75%, 57%, and 92%, respectively.

**Discussion**

Systemic therapy of advanced cancer has been revolutionized by the advent of novel targeted therapeutics, which are associated with prolongation of survival and improvement in quality of life. The application of these therapies to patients with BM requires an understanding of their clinical pharmacology, efficacy, and safety as it relates to the CNS. Unfortunately, patients with active BM have generally been excluded from clinical trials of novel targeted therapies because of the concern for unexpected toxicities and the likelihood that the poor survival of patients with BM will reduce the effect size between comparator agents. Although knowledge about the efficacy and safety of targeted therapies for BM had previously been limited to retrospective observations and small prospective studies, that trend appears to be changing with increasing investigation of these novel therapies in prospective studies specifically for patients with BM.

The few single-arm phase 2 studies that have focused on targeted therapy in patients with BM from NSCLC, breast cancer, or melanoma highlight the potential of targeted systemic therapy to address intracranial disease. There are encouraging findings regarding the utility of the EGFR TKIs gefitinib and erlotinib in BM from EGFR-mutant tumors and the second-generation ALK TKIs ceritinib, alectinib, and brigatinib in BM from ALK-positive disease. Similar findings are evident with use of anti-HER2 targeted therapies trastuzumab, lapatinib, and T-DM1 for BM from HER2-overexpressing breast cancer, although efficacy is improved when capecitabine is added to either trastuzumab or lapatinib. The BRAF and MEK inhibitors, either alone or in combination, appear active in patients with BRAF-mutant melanoma. Various studies have reported intracranial response rates ranging from 31% (with dabrafenib in BRAF V600E-mutant melanoma) to as high as 75% (with erlotinib in EGFR-mutant NSCLC).\textsuperscript{35,40,67,131,164} Unfortunately intracranial responses with many of these drugs may not be as robust as extracranial responses, perhaps reflecting insufficient drug concentrations in brain tissue. Responses with these therapies are generally of quick onset but may not always be durable. Monotherapy with a TKI and close monitoring for progressive disease is a reasonable strategy for patients with small volume, asymptomatic BM associated with appropriate molecular subgroups of these diseases.

Emerging data suggest that immunotherapy with monoclonal antibodies that target the PD-1 or CTLA-4 pathways may lead to substantial and durable intracranial responses concordant with their systemic activity. This may be because immune checkpoint inhibitors do not require direct access to brain parenchyma, as their effects are mediated by proxy on peripheral T cells, which in turn penetrate into the CNS. The hallmark of successful immunotherapy is the potential for durable responses and long-term survival in responding patients, which appears to be preserved in patients with BM. Immunotherapy often has
a delayed onset of response and may lead to inflammatory treatment effects, which are highly relevant to the patients with BM at risk of neurologic complications due to increased mass effects.

Given the aforementioned advances, there is increasing recognition of the need to include patients with untreated BM in clinical trials and to perform trials of systemic therapy specifically in patients with BM. This strategy is not without its challenges because such trials are intensive, expensive, and come with a risk of neurologic complications. However, such studies are required to determine the optimal combination of targeted treatments and traditional therapies used to treat patients with BM.

In conclusion, the emerging evidence for the potential of novel targeted therapies that successfully target BM from NSCLC, breast cancer, and melanoma represents a paradigm shift in the management of BM. Patients with BM increasingly have a realistic hope that current targeted therapies and further research into new targeted therapies will permit an improvement in both their survival and quality of life.

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