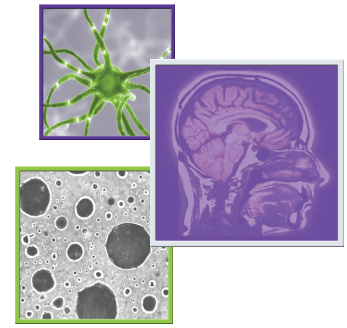
REVIEW

CNS Oncology



Immunotherapy and targeted therapy in brain metastases: emerging options in precision medicine

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Practice points

- The approach to brain metastases (BM) is multidisciplinary and includes surgery, radiation therapy/stereotactic radiosurgery, whole-brain radiation therapy and systemic therapy. Targeted therapies are playing an increasingly important role in the management of BM. Genetic characterization of BM is revealing new insights into potential therapies for BM patients.
- Lung cancer BM: EGFR ± T790M, ALK.
- Second-generation tyrosine kinase inhibitors (TKIs), including afatinib, have activity in EGFR-positive non-small-cell lung cancer BM. Patients on first-generation TKIs at CNS progression should be transitioned to a second- or third-generation EGFR TKI.
- In patients with anaplastic lymphoma kinase-positive non-small-cell lung cancer BM, newer generation anaplastic lymphoma kinase TKIs such as ceritinib and alectinib have demonstrated greater intracranial response rates than first-generation TKIs.
- Breast BM: HER2, BRCA 1/2 (as well as hormone receptors).
- Dual HER2 and EGFR TKIs, like lapatinib, have modest CNS activity. The combination of capecitabine and lapatinib has higher response rates.
- Melanoma BM: BRAF, PD-L1 expression.
- BRAF inhibitors, like vemurafenib and dabrafanib, have been shown to have good CNS response rates, and should be used concurrently with MEK inhibitors.
- Early studies have shown that anti-CTLA-4 antibodies, such as ipilimumab, and anti-PD-1 antibodies, such as pembrolizumab, have activity in CNS metastatic disease.

Brain metastases (BM) continue to represent an unmet clinical need in oncology. Immunotherapy and targeted therapy hold great promise in the treatment of BM. Emerging data are confirming the activity of these agents in patients with BM. Genomic studies have confirmed that clinically actionable mutations are present in BM and they can be used in clinical studies to link targeted therapies with their genetic targets. Furthermore, as molecular signatures associated with sensitivity and resistance to immunotherapies are developed, we will better be able to select BM patients who will most benefit from these therapies. Understanding the genetic and immune evolution within BM should drive the next generation of immunotherapy and target therapy, as well as increase the accuracy of the selection process for these therapies.

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Metastasis to the brain is one of the most common causes of neurological complications in systemic cancers, occurring in 20–40% of patients during the course of the disease [1,2]. The annual incidence of brain metastases (BM) has been estimated to be 8–10% of patients with cancer, with increasing incidence over time as neuroimaging modalities improve and the treatment of disseminated disease becomes more effective in increasing survival [1,3–5]. Moreover, BM are the most common intracranial tumors in adults, accounting for over half of brain tumors [6,7]. Two large population studies, one conducted in the Detroit Metropolitan area, the other in the Netherlands, found that lung, melanoma, renal cell, breast and colorectal cancers made up greater that 67% of the cumulative incidence of BM [1,3]. Both studies estimated the cumulative incidence of BM at 5 years to be 16–20% for lung cancer, 7% for melanoma, 7–10% for renal cell cancer, 5% for breast cancer and 1–2% for colorectal cancer. The treatment of all BM in general usually comprises of some combination of surgery, radiation therapy (RT) and systemic chemotherapy; however, new targeted therapies for each of these tumor types may start to find a place in the repertoire, as therapies are adapted to the unique genetic mutations of each type.

The approach to treatment of BM is strongly influenced by prognosis. Predictors of longer survival include higher performance status, younger age, well-controlled primary tumor activity, absence of extracranial metastases and low tumor burden; though patients with four or more BM seem to represent a group with an invariably poor prognosis [8–10]. For patients with favorable prognoses and limited number of metastases (1–3), surgical resection and stereotactic radiosurgery (SRS) are considered the standard of care to achieve better control and reduction in tumor burden, although no prospective randomized studies comparing definitive SRS to surgery have been carried out. In these patients, a meta-analysis demonstrated an improved survival, reduced morbidity and decreased local recurrence with surgical resection added to radiotherapy, compared with whole-brain radiation therapy (WBRT) alone, although several of the trails in the analysis did not reach statistical significance [11–14]. In patients with solitary BM who have undergone surgical resection, new evidence favors SRS to the resection cavity, associated with far less neurotoxicity than WBRT [15].

Despite advances in surgical techniques and radiotherapy, even patients with optimal risk factors have median survival of 7.1 months, although these numbers do not reflect treatment in the era of targeted and immunotherapy [8,16]. In patients with multiple BM considered to have advanced disease and poorer prognoses, treatment is often aimed at palliation and symptom control. WBRT remains the standard of care for these patients. Chemotherapy has historically been used in the recurrent setting, or in the primary treatment of chemosensitive tumors, such as germ cell tumors [17]. Nonetheless, previous data are limited to offer any definitive conclusion of the role of chemotherapy in newly diagnosed BM. In several randomized prospective trials, primary chemotherapy and groups of primary chemotherapy with delayed WBRT had similar response rates and survival outcomes to WBRT alone [18,19]. Other trials of concurrent chemotherapy with WBRT and radiosensitizing agents during WBRT have found some improved response rates; however, no survival benefit was demonstrated and there were significantly increased rates of acute and latent sequalae of WBRT [20–22]. Thus, concurrent, nontargeted chemotherapy with WBRT has been discouraged.

The role of immunotherapy and targeted therapy is becoming more well established in the treatment of BM as cancers are getting more genetically defined. Advances in molecular genetics have led to a better characterization of the genetic heterogeneity of BM and the detection of unique drivers [23]. The concept of divergent or branched evolution of metastases from their primary tumors is just beginning to play a role in the treatment of BM and in the understanding of their unique clinical features. In this review, we discuss how the genomic context of BM plays a role in the treatment of several of the most common cancers to metastasize to the brain, with the goal of informing rational therapy options.

Non-small-cell lung cancer

Lung cancer is the leading cause of cancer mortality worldwide, accounting for 18.2% of total deaths from cancer [24]. It is also the most common primary malignancy to metastasize to the brain, with non-small-cell lung cancer (NSCLC) constituting the majority of cases [25]. BM occurs in approximately 7.4% of NSCLC patients at presentation, and 25–30%

will develop BM during the course of their disease [26,27]. Current treatment regimens utilizing platinum-based chemotherapy, radiation and surgical measures afford patients with stage III NSCLC – a 26.1% 5-year survival rate; however, stage IV disease remains challenging, with a 1-year survival rate of 10% [28]. In addition, many patients with complete initial responses to therapy will develop BM, with an incidence of 40–50% at 3 years [29]. Given this, targeted therapies, especially in tumors with activating mutations in *EGFR* and *ALK*, have been recognized to significantly improve clinical outcomes compared with previous platinum-based chemotherapy, and have thus become the standard of care in metastatic lung cancer [30,31].

Activating mutations in the tyrosine kinase domain of the EGFR are present in 10–25% of NSCLC, with the highest prevalence found in adenocarcinomas of never-smoking women of East Asian descent [29]. Moreover, the frequency of BM was higher among *EGFR*-mutated cases than *EGFR* wild-type cases, at 31.4 versus 19.7% (odds ratio [OR]: 1.86; 95% CI: 1.39–2.49; $p < 0.001$) [32]. In the past 10 years, many randomized control trials have established that EGFR tyrosine kinase inhibitors (TKIs) improve progression-free survival (PFS) and overall survival (OS) compared with standard platinum-based chemotherapy in patients without BM [33]. As a result, the *EGFR* mutation is associated with prolonged survival after diagnosis of BM (hazard ratio [HR] 2.23; 95% CI: 1.62–3.10; $p < 0.001$) [32].

Fusion of the ALK and EML4 results in an oncogenic chimeric protein with constitutive kinase activity, and occurs in 2–8% of patients with NSCLC [34]. Like EGFR mutations, ALK-rearranged NSCLC are most frequent in adenocarcinomas of young, never-smoking patients [35]. BM are found in 23–31% of ALK-positive patients [34]. Unlike EGFR-mutant NSCLC, however, ALK activation has not been found to increase the risk of BM [35]. Nonetheless, ALK inhibitors are under constant investigation in the treatment of BM, given their success in the control of primary ALK-mutant NSCLC [36].

Although genetically driven therapies have made tremendous progress in this disease, BM are still quite frequent in advanced EGFR-mutated or ALK-rearranged NSCLCs, with an estimated 45% of patients with involvement of the CNS by 3 years of survival. Issues of brain penetration and insufficient therapeutic levels of systemic agents in cerebral spinal fluid (CSF) are frequently cited; new data are also emerging that BM harbor additional oncogenic drivers [23]. Overall, these data points toward the important need to systematically investigate these drug therapies, to meet the clinical needs of the ever-evolving schema of personalized care in NSCLC [37].

• NSCLC: EGFR tyrosine kinase inhibitors

Overall, the superiority of first- and second-generation TKIs to chemotherapy in EGFR-mutant NSCLC is well established and has led to regulatory approval of these drugs as first-line therapies [19,38–39]. Gefitinib and erlotinib were the first US FDA-approved EGFR TKIs. Unfortunately, resistance to these first-generation agents inevitably occurs, most commonly the threonine-to-methionine substitution at position 790 on exon 20 (T790M) [40,41]. Third-generation TKIs have been developed to more effectively combat these resistant EGFR-mutant types, such as osimertinib and rociletinib. In Phase II trials, these TKIs have been shown to have an objective response rate (ORR) of 51–64% in resistant EGFR-mutant NSCLC [42–44].

There have also been recent data comparing first- and second-generation TKIs from the LUX-Lung 7 trial suggests a superiority of afatinib to gefitinib in treatment naive patients, with a more tolerable side effect profile [45,46]. Other trials are ongoing, comparing the efficacy of other first-, second- and third-generation TKIs [47,48,49,50].

Overall, the evidence for EGFR TKIs in BM is hopeful but lacking. One prospective trial exploring EGFR TKIs in BM in 28 patients has preliminarily reported an 83% ORR with first-generation EGFR TKIs [51]; however, other trials report more modest responses [52,53]. One of the primary reported issues in the use of EGFR TKIs in the treatment of BM is their inconsistent penetration of the blood–brain barrier (BBB). In one study, the CSF penetration rate of erlotinib in patients with CNS metastases was found to be 5.1%, and had a significantly lower concentration in the CSF than in the plasma [54]. Pulsatile, weekly high-dose erlotinib has been suggested to overcome this limitation, and it has been shown to be effective in a retrospective trial; however, more prospective trials must be done before any conclusion can be made about its effect on OS [55,56]. Lastly, a recent study of CSF concentrations of afatinib has suggested

better overall CNS activity of next-generation EGFR TKIs [57].

Other trials have studied the sequence of EGFR TKI and RT. With the goal of reducing potential toxicities of RT, there has been increasing interest in deferring RT with upfront EGFR TKI therapy in those patients that develop BM. One retrospective study of upfront EGFR TKI with deferred RT (SRS or WBRT) found that OS was decreased in the upfront EGFR TKI cohort [58]. There is currently a randomized control trial studying the use of upfront erlotinib with RT at the time of brain tumor progression, versus the standard of erlotinib with concurrent RT [59]. It is also unclear what the correct sequence of WBRT is with EGFR TKIs, as it is unclear whether upfront RT has a benefit [60,61]. One recent retrospective study of 230 EGFR-mutant NSCLC patients with BM concluded that EGFR TKIs plus WBRT did not have any survival benefit compared with upfront EGFR TKIs alone [62].

• NSCLC: ALK tyrosine kinase inhibitors

First-generation ALK TKIs, such as crizotinib, have been shown to be superior to chemotherapy as first-line treatment of patients with ALK-rearranged NSCLC [63,64]. Ceritinib, a second-generation ALK TKI, has been also been shown to be effective, especially in crizotinib-resistant cases [65–67]. The ASCEND-1 trial, a Phase I trial of ceritinib in ALK TKI-naive and ALK TKI-pretreated patients, has shown a 56% overall response in ALK TKI-pretreated patients [68]. Another multicenter retrospective study reported greater OS with sequential crizotinib and ceritinib in patients with and without resistant ALK NSCLC [67]. These two studies have opened the discussion as to the most effective sequence and duration of ceritinib in ALK TKI-naive and previously treated patients.

Even with modern therapies, ALK-rearranged NSCLC often progresses in the CNS. Within 1 year from diagnosis, the incidence of BM is 23.8%, increasing to 45.5 and 58.4%, at 3 and 5 years, respectively [37]. In one retrospective pooled analysis of the PROFILE 1005 and 1007 trials, 20% of patients on crizotinib developed BM at progression [69]. On the other hand, the subset of patients that were ALK TKI-naive attained initial CNS disease control rates of 56% at 12 weeks on crizotinib, with a median intracranial time to progression of 7 months for those with untreated BM and 13.2 months in those with previously treated BM. The failure of crizotinib in ALK TKI-naive patients, as well as ALK TKI-pretreated patients seems to be explained in part by resistance and poor penetration across the BBB [70]. Fortunately, newer generations of ALK TKIs have shown efficacy in resistant ALK-rearranged NSCLC, as well as better CNS activity [71,72]. Alectinib is one such next-generation ALK TKI that has demonstrated excellent CNS activity, with intracranial response rates as high as 75% and a median intracranial duration of response of 10–11 months [71,72]. The ASCEND-1 trial also retrospectively looked at 94 patients with BM and found that 79% of ALK TKI-naive patients had an intracranial response to ceritinib, as well as 65% of ALK TKI-pretreated patients [68]. It is also clear from several studies that ALK TKIs add to OS in combination with RT, although the toxicity of the combination has yet to be full investigated [73,74].

• NSCLC: bevacizumab

Bevacizumab is a monoclonal antibody against the VEGFR and has shown to be beneficial in a variety of tumors. The Eastern Cooperative Oncology Group conducted a landmark randomized trial of 878 patients with advanced NSCLC to explore its potential impact on OS [75]. The study randomized these patients into two arms of standard chemotherapy (paclitaxel-carboplatin) and chemotherapy plus bevacizumab, and found that chemotherapy plus bevacizumab showed a greater OS (12.3 vs 10.3 months; HR for death: 0.79; p = 0.003). Although this study shows a promising role for bevacizumab for advanced primary NSCLC, it was not able to comment specifically about BM, as patients with metastatic CNS lesions were excluded from the trial due to the concern for increased risk of intracranial hemorrhage. Other studies since then have postulated that bevacizumab may be safe in patients with BM, but there have not been any definitive prospective studies done to confirm its safety or efficacy in BM [76,77]. One retrospective study of 776 patients with BM from NSCLC showed that standard chemotherapy plus bevacizumab was better overall than chemotherapy alone or TKIs alone [78]. Furthermore, the authors also found that the median OS and PFS in those with EGFR-mutated NSCLC, EGFR TKIs were not superior to chemotherapy plus bevacizumab. In an analysis of three Phase III trials, another retrospective study also hypothesized that

pretreatment of bevacizumab may prevent BM in patients with lung adenocarcinomas, which was shown in mouse models [79].

Breast cancer

Breast cancer is the second most common cause of cancer-related death in women [80]. It is also the second most common cancer to metastasize to the brain [3]. Although the overall prognosis for nonmetastatic breast cancer is considered quite good, advanced disease is still somewhat poorly controlled, with the 26.3% 5-year survival for patients with distant metastases [81]. The overall incidence of BM in breast cancer is approximately 2.5–3%, but seems to be increasing as women live longer with modern therapies [3,82]. Moreover, HER2-enriched breast cancers, triple-negative breast cancer (TNBC) and basal-like subtypes of breast cancer are associated with increased risk of developing BM at disease progression, and have represented uniquely challenging clinical complications [83].

HER2 overexpression is seen in roughly 20% of patients with breast cancer [84]. Moreover, BM develop in 30–50% patients with HER2-positive breast cancer [82,85]. Although OS seems to be better in patients with BM that are HER2-positive than other breast cancer subtypes since the development of HER2 receptor inhibitors, such as trastuzumab, the risk of BM from HER2-postive disease is higher [83,86]. There is also evidence to suggest that BM occur in patients with HER2-postive breast cancer that is otherwise systemically well controlled with HER2-specific therapy [87]. Furthermore, HER2-positive status may increase resistance to endocrine therapies in hormone-sensitive breast cancers [88]. Therefore, it is especially important that new therapies be developed to prevent the progression of this disease.

TNBC is another especially challenging disease in which BM are relatively common. In one retrospective study of 679 women with nonmetastatic TNBC, the cumulative incidence of BM was 5.6% in 2 years and 9.6% in 5 years, with the greatest risk of BM occurring in those that presented with more advanced disease [89]. Furthermore, the estimated OS of patients of TNBC who have developed BM is 5 months [90,91]. To date, systemic treatment has been largely ineffective; however, there has been a growing pool of novel targets since the advent of gene sequencing in these cancers. Several pathways that have been under investigation involve the BRCA and PARP, which are components of major DNA-repair pathways. In a landmark experiment by Farmer *et al.*, it was found that BRCA1- and BRCA2-deficient cells were extremely sensitive to PARP [92]. In addition, histological studies have shown an overlap between the pathological and clinical features of TNBC and basal-like breast cancers and BRCA-associated cancers, which have shown some promise in targeting these types of tumors [93].

Recent evidence suggests a genotypic and phenotypic divergence of BM compared with breast cancer primary tumors. One example is a study that showed a loss of hormone receptor expression in BM compared with their hormone-sensitive primaries [94]. In addition, whole exome analysis of a large cohort of BM from breast cancer demonstrated branched evolution in every case, meaning that BM and their matched primary tumors shared a common ancestor, but there was continued genetic evolution in the BM, with new clinically actionable mutations in the BM. Furthermore, clinically actionable mutations in the cyclin-dependent kinase and PI3K/AKT/mTOR pathways were common in BM [23]. Therapies targeting mTOR and PI3K signaling have been investigated [95,96]. Taken together, these findings suggest a role in the genomic profiling of BM when there is tissue available as part of clinical care in guiding therapy options [23].

• Breast cancer: HER2 antibodies

Trastuzumab, a monoclonal antibody targeting the extracellular domain of HER2, had revolutionized the treatment of breast cancer, leading to significant improvements in PFS and OS in patients with HER2-positive breast cancer [97]. Unfortunately, recurrence often occurs, and BM can develop in up to 35% of women being treated with adjuvant trastuzumab [87,97–99]. One meta-analysis of 9000 women found a 2.56% increased risk of BM at first occurrence compared with 1.94% in matched controls [100]. The propensity of BM to occur during trastuzumab therapy has often been postulated to be due to inherent biological factors and the poor CNS penetration of trastuzumab, creating a CNS sanctuary effect [85,98]. Similar increases in the incidence of BM are seen with the use of pertuzumab, a related HER2 dimerization inhibitor [101].

This issue of increased BM with HER2 inhibitors was also addressed in the CLEOPATRA trial, which suggested that the combination of

pertuzumab, trastuzumab and docetaxel delayed onset of new CNS disease (HR: 0.58; p = 0.0049) in HER2-positive patients, compared with placebo, trastuzumab and docetaxel; however, OS was not significantly different between the two groups [101]. Other supporting evidence for the use of pertuzumab-containing regimens in BM from HER2-postive breast cancer is offered in several recent case reports, but no prospective studies qualifying this evidence exist [102,103]. There are also studies with the antibody-cytotoxin conjugate, trastuzumab-emtasine (T-DM1) that have shown activity in non-CNS metastatic disease and retrospective studies show activity in the CNS [104], but robust evidence for its efficacy in CNS disease is lacking [105,106].

• Breast cancer: HER2 TKIs

Lapatinib is a dual HER2 and EGFR TKI that has shown modest CNS antitumor effects in adjuvant monotherapy, with a CNS ORR of 6% [107]. The Phase II LANDSCAPE trial also explored lapatinib in combination with capecitabine and found a CNS ORR of 20% [107]. Further investigation of lapatinib and capecitabine in patients with HER2-postiive breast cancer that had previously received chemotherapy and RT showed a CNS ORR ranging from 21 to 38% [108,109]. Additionally, lapatinib and capecitabine have also yielded CNS ORR as high as 65% in treatment-naive patients with HER2-positive breast cancer [110]. Lastly, Lin *et al.* also studied lapatinib with topotecan and found that the combination was not active and associated with excess toxicity, suggesting some unique CNS activity of capecitabine [109].

Neratinib, an irreversible HER1, HER2 and HER4 TKI, has also shown activity in patients with HER2-positive metastatic breast cancer [111]. In one multicenter Phase II study, two cohorts of patients with metastatic HER2-positive breast cancer with and without prior trastuzumab were given neratinib, resulting in ORRs of 24 and 56%, respectively [111]. Another Phase II trial of neratinib versus placebo in patients with early-stage HER2-positive disease who completed at least 1 year of prior trastuzumab treatment showed a 2-year PFS rate of 93.9% for the neratinib group [112]. Furthermore, in those patients that did have recurrence of disease, the incidence of BM was not significantly different between the neratinib and placebo arms. Indeed, the NEfERTT trial of patients with metastatic HER2-postive breast cancer given neratinib and paclitaxel showed significantly lower rates of CNS progression than trastuzumab and paclitaxel, although the two groups had similar efficacy on OS [112,113].

• Breast cancer: PARP inhibitors

PARP inhibitors theoretically function to select for normal cells by crippling DNA repair in BRCA or PARP-mutant cells [114]. Preliminary results have found that PARP inhibitors have activity in BRCA1/2-deficient breast cancers, which include a subset of TNBC [115,116]. Olaparib has had modest effects on OS in advanced TNBC and failure has been attributed to the development of resistance and the fact that sporadic TNBC tumor cells may not all harbor BRCA mutations [115]. For these cases that are BRCA wild-type, one experimental model suggested that PI3K inhibitors may sensitize TNBC cells to PARP inhibitors [96]. Further investigation of olaparib in combination with PI3K inhibitor, PI-103, has shown that the combination can also serve as radiosensitizers and lead to significantly reduced tumor volume in radiation-treated xenograft models [117].

To date, not many studies have directly measured the effects of PARP on BM in TNBC. In mouse models, one recent experiment showed that carboplatin and PARP inhibitor ABT888 penetrates the BBB and improves OS in BRCA-mutant intracranial models but not in BRCA wild-type models, further confirming the issue of BRCA-proficient TNBC [118]. On the other hand, one recent Phase I study of 25 breast cancer patients with BM has suggested that veliparib, a novel PARP inhibitor, may improve survival by its ability to cross the BBB and further act as a radiosensitizer when paired with WBRT [119]; but the specific subtypes of breast cancer for these patients were not delineated. Taken together, these studies suggest the need for some combination of CNS active PARP inhibitors with RT in prospective trials. Ultimately, more studies are needed to investigate the efficacy of PARP inhibitors in BM and resistance of TNBC to PARP inhibitors [115].

Melanoma

Melanoma is the third most common primary tumor to metastasize to the brain [3]. Moreover, up to 75% of patients with metastatic melanoma will develop BM during the course of their disease, with CNS disease present in 20% of patients at diagnosis [1]. Unfortunately, the prognosis of metastatic melanoma with CNS

involvement is still quite poor. Median OS after the diagnosis of BM has historically been around 4.7 months [120]; although, a recent retrospective analysis suggests that median OS has reached about 7.7 months with the use of immunotherapies and BRAF inhibitors [121].

Approximately 50% of patients with metastatic melanoma will have an activating mutation of the BRAF oncogene leading to downstream constitutive activation of the MAPK signaling pathway, of which 95% of cases are V600E mutations [122]. BRAF inhibitors are FDA-approved for metastatic melanoma, improving the prognosis in these patients. However, some studies suggest that BRAF-mutant melanoma carries a higher risk of developing BM.

Immune checkpoint inhibitors have also proven to play a significant role in treating metastatic melanoma, which include anti-CTLA-4 and anti-PD-1 receptor antibodies. These agents essentially function to activate the immune system and augment the antitumor response [123–125]. Although their efficacy has been studied in a number of cancers, several of these agents have been FDA-approved for the treatment of advanced melanoma, and thus will be discussed here.

• Melanoma: BRAF inhibitors

Overall BRAF inhibitors like vemurafenib and dabrafanib have markedly improved OS in patients with advanced melanoma [126,127]. The evidence for their activity in BM, however, has been largely lacking, since many large trials excluded CNS disease [128]. One retrospective study found that BRAF inhibitors were associated with a lower incidence of BM in patients with BRAF-mutant melanoma with no prior history of BM; however, BRAF inhibitors had no effect on PFS and OS in patients who had developed BM prior to treatment [129]. In a prospective multicenter Phase II trial of 172 patients with BM due to BRAF-mutant melanoma, intracranial response rates of dabrafinib were recorded in 39.2% of treatment-naive patients, and 30.8% of previously treated patients (but without prior systemic treatment) [130]. In addition, the study corroborates the Phase I safety profile of dabrafinib [131]. Nonetheless, median PFS and OS in BRAF-mutant melanoma patients with BM have been approximately 4 and 5 months, respectively [130–132].

To prevent resistance, BRAF inhibitors are commonly combined with MEK inhibitors like trametinib and cobimetinib, which inhibit MEK, a downstream kinase from BRAF in the MAPK pathway [133,134]. However, evidence is scarce in support of its benefit in BM, again because of the lack of randomized clinical trials exploring the combination [135].

• Melanoma: anti-CTLA-4 antibodies

Ipilimumab is an FDA-approved anti-CTLA-4 antibody for metastatic melanoma. Overall, the systemic response rates in patients with melanoma have ranged from 11 to 21%, with higher response rates in patients with BRAF wild-type melanoma with PD-L1 expression [136,137]. Moreover, OS in melanoma patients with BM on ipilimumab appears similar to those patients without CNS involvement [138]. Furthermore, several studies have shown robust, long-term responses with ipilimumab use, on the order of years [138,139]. Other studies have suggested that ipilimumab also significantly increases OS in conjunction with SRS [140,141]. One retrospective analysis found that the 2-year survival rate of those receiving SRS plus ipilimumab was 47.2%, compared with 19.7% in patients that received SRS alone [141].

Exome sequencing of tumors from patients with melanoma who have received anti-CTLA-4 therapies are currently being carried out [125]. Snyder *et al.* characterized collections of somatic mutations in 64 melanoma exomes with the hypothesis that they may ultimately help predict response to anti-CTLA-4 therapy and were able to identify mutational profiles that were associated with better prognoses. More clinical data are needed to support this finding, especially in patients with BM.

• Melanoma: anti-PD-1 antibodies

Nivolumab and pembrolizumab are recently FDA-approved PD-1 checkpoint inhibitors superior to ipilimumab in systemic response rates, with ORR ranging from 33 to 57% [136,142]. Although direct evidence for PD-1 checkpoint inhibitors in BM is still lacking, there are studies to suggest improved OS when used with SRS. One trial of 26 patients with melanotic BM estimated an 85% sustained disease control at 12 months [143]. In addition to clinical efficacy, the safety of PD-1 checkpoint inhibitors must also continue to be investigated, as there are several early reports of nivolumab-induced organizing pneumonia and CNS demyelination [144,145]. Nonetheless, studies such as the NIBIT-M2 trial are currently comparing PD-1 checkpoint

Table 1. Select studies of newer targeted therapies and immunotherapies in brain metastases.

Cancer type	Mutation status	Study (year)	Intervention (dose in mg, p.o. unless otherwise specified)	PFS in months (95% CI)	CNS response rate (partial or complete)	Ref.
NSCLC	*EGFR*	Jänne *et al.* (2015)	Osimertinib (20–240 mg q.d.)	9.6 (8.3 to not reached) in T790M-positive patients; 2.8 months (2.1–4.3) in T790M-negative patients	–	[43]
		He (2015)	Rociletinib (Free base 900 mg b.i.d. or with hydrogen bromide salt)	13.1 (5.4–13.1) in T790M-positive tumors; 5.6 (1.3–not reached) in T790M-negative patients	–	[42]
		Porta *et al.* (2011)	Erlotinib (150 mg q.d.)	2.9 (2.3–3.5)	82.40%	[52]
	ALK	Shaw *et al.* (2014)	Ceritinib (400 mg q.d.)	7.0 (5.6–9.5)	–	[65]
		Shaw *et al.* (2016)	Alectinib (600 mg b.i.d.)	8.1 (6.2–12.6)	75%	[72]
	Unspecified	Sandler *et al.* (2006)	Bevacizumab (15 mg/kg iv.) + paclitaxel- carboplatin (200 mg/m^2 to 6 mg/ml/min iv.)	6.2 (0.57–0.77)	–	[75]
Breast	*HER2*	Swain *et al.* (2014)	Pertuzumab (840 mg) + trastuzumab (429 mg) + docetaxel (8 mg/kg)	15 (0.39–0.85)	–	[101]
		Lin *et al.* (2009)	Lapatinib (1250 mg) + capecitabine (2000 mg/m^2)	–	20%	[107]
		Burstein *et al.* (2010)	Neratinib (240 mg q.d.)	3.1 (not reported)	–	[111]
	TNBC	Anders *et al.* (2010)	Olaparib (400 mg b.i.d.)	5.7 (4.6–7.4)	–	[115]
Melanoma	*BRAF*	Long *et al.* (2012)	Dabrafinib (150 mg b.i.d.)	16.6 (15.7–21.9)	39.2% (in treatment-naive patients)	[130]
	PD-L1 expression	Larkin *et al.* (2015)	Ipilimumab (3 mg/kg every 3 weeks per cycle) + nivolumab (1 mg/kg every 3 weeks per cycle)	11.5 (4.3–9.5)	–	[136]
	Unspecified	Goldberg *et al.* (2016)	Pembrolizumab (10 mg/kg)	–	22%	[148]

PFS was focused in this analysis, since many of the trials mentioned did not have mature enough data to comment on overall survival.
ALK: Anaplastic lymphoma kinase; b.i.d.: Twice daily; HER2: Human epidermal growth factor receptor 2; iv.: Intravenously; NSCLC: Non-small-cell lung cancer; PD-L1: Programmed death-ligand 1; PFS: Progression-free survival; p.o.: By mouth; q.d.: Once daily; TNBC: Triple-negative breast cancer.

inhibitors to currently approved standards [146], while other ongoing trials are evaluating their activity and safety [147]. Furthermore, an early analysis of pembrolizumab in BM from melanoma (n = 18) and NSCLC (n = 18) showed promising activity [148].

Conclusion

Immunotherapy and targeted therapy hold great promise in the treatment of BM (see **Table 1** for a summary of the pertinent therapies discussed above). With each passing year, molecular genetic studies elucidate the roles of these agents in the contemporary approach, many of which have benefits in primary and intracranial sites of disease [23]. Furthermore, as molecular signatures associated with sensitivity to immunotherapies are developed, we will better be able to select patients who will most benefit from these therapies. Finally, understanding the genetic evolution of BM from primary tumors should drive the development of rational clinical trials for this common and devastating complication of cancer.

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