Medical management of brain metastases

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Abstract
The development of brain metastases occurs in 10–20% of all patients with cancer. Brain metastases portend poor survival and contribute to increased cancer mortality and morbidity. Despite multimodal treatment options, which include surgery, radiotherapy, and chemotherapy, 5-year survival remains low. Besides, our current treatment modalities can have significant neurological comorbidities, which result in neurocognitive decline and a decrease in a patient’s quality of life. However, innovations in technology, improved understanding of tumor biology, and new therapeutic options have led to improved patient care. Novel approaches in radiotherapy are minimizing the neurocognitive decline while providing the same therapeutic benefit. In addition, advances in targeted therapies and immune checkpoint inhibitors are redefining the management of lung and melanoma brain metastases. Similar approaches to brain metastases from other primary tumors promise to lead to new and effective therapies. We are beginning to understand the appropriate combination of these novel approaches with our traditional treatment options. As advances in basic and translational science and innovative technologies enter clinical practice, the prognosis of patients with brain metastases will continue to improve.

Keywords
brain metastases | immunotherapy | radiation | surgery | targeted therapy.

An estimated 10–20% of patients with cancer will be diagnosed with brain metastases over their disease course. However, the true incidence is likely higher as autopsy studies have reported metastases in 30–40% of patients with cancer. As advances in therapy lead to prolonged survival after the initial cancer diagnosis, clinical trial enrollment increases, increasing the frequency of staging MRIs, reported incidence of brain metastasis will likely continue to increase. Brain metastases generally portend a poor prognosis and even those with the most favorable prognostic factors have an overall 2-year and 5-year survival of 8.1% and 2.4% across all primary tumors. While traditional treatment options including surgery and radiotherapy remain standard approaches for treating brain metastases, advances in targeted therapeutics and immunotherapies and providing exciting new treatment options for these patients.

Epidemiology
The three most common primary tumors associated with brain metastases, and the primary focus of this review, are lung (20–56%), breast (5–20%), and melanoma (7–16%) accounting for 67–80% of all brain metastases. Within each primary tumor, the molecular subtype and previous treatments also play a role in the incidence of brain metastases. For example, in non-small-cell lung cancer (NSCLC), about 25–40% of patients will develop brain metastases, but in patients with anaplastic lymphoma kinase (ALK) rearrangements that have failed first-line ALK inhibitors, the incidence of brain metastases is between 45% and 70%. In addition, in breast cancer, women with human epidermal growth factor receptor 2 (ERBB2 or HER2) amplification or triple-negative hormone receptor status are at a higher risk of developing brain metastases compared to women with ER-positive or PR-positive cancers. The risk of developing brain metastases also increases with more advanced primary disease. In HER2-positive breast cancer, the incidence of brain metastases increases from 1.1% to 11.5% in patients with distant metastases compared to those without. The risk of brain metastases also varies by age and is dependent on the primary tumor location. For breast cancer the risk is highest in younger patients.
between 20 and 39, in lung cancer the highest risk is between 40 and 49, whereas in melanoma, renal cell carcinoma (RCC), and colorectal cancer the highest risk is between 50 and 59. Together this epidemiological data highlight the different trends in brain metastases across primary tumor types as well as the unique characteristics of each.

**Prognosis**

Patients with brain metastases have a dismal prognosis with 2-year and 5-year overall survival of 8.1% and 2.4% across all primary tumors. Various prognostic scores have been developed to classify the disease severity and guide the aggressiveness of therapy, including inclusion in clinical trials. In 2008, a prognostic score was developed that analyzed 1960 patients and took into account additional clinical variables. In the graded prognostic assessment (GPA), patients are given a score based on age, KPS, number of central nervous system (CNS) metastases, and the presence or absence of extracranial metastases. The GPA splits patients into 4 different groups, those with the best score having a median survival of 11 months compared to those with the worst score have a prognosis of 2.6 months. This score remained the standard until the advent of targeted therapeutics shifted the treatment of lung cancer brain metastases and the GPA no longer predicted survival in these patients. Therefore, a lung-specific GPA that took into account the molecular profile of the tumors (Lung-molGPA) was developed. Additional prognostic scores have also been developed and the constant in all of these is the inclusion of KPS. Similar GPA scores exist for melanoma, RCC, and breast cancer brain metastases. Finally, a nomogram for predicting individual survival probabilities has been developed utilizing the Radiation Therapy Oncology Group (RTOG) database.

**Overview of Treatment Options**

Surgery and radiotherapy have long been the cornerstone for the management of brain metastases. Until recently, systemic drug therapies have shown limited efficacy in the management of brain metastases. Lack of permeability of drugs through the blood–brain barrier (BBB) is often thought to be one reason for this low efficacy.

Even temozolomide, which is standard of care for patients with glioblastoma, has shown marginal benefit in the treatment of brain metastases. As a single agent, the overall response rate intracranially of temozolomide for brain metastases was less than 10% across multiple primary tumor types. Additionally, temozolomide has minimal efficacy on the primary tumor, with extracerebral response rates ranging from 3% to 43% depending on the primary tumor.

Similarly, chemotherapies given for the primary tumor demonstrate very little intracranial efficacy. However, as discussed below, advances in immunotherapy and targeted therapies are beginning to demonstrate intracranial efficacy (Table 1).

**Whole-Brain Radiation Therapy**

Historically, whole-brain radiation therapy (WBRT) was the standard treatment for most patients with brain metastases. Two trials in the early 1990s demonstrated that surgery in addition to radiation provided survival benefits and improved local control. WBRT has remained the most commonly used treatment for brain metastases due to its accessibility, quick initiation, the ability to control visible and occult lesions, as well as symptom improvement. However, in the last decade, the use of WBRT has been decreasing. This is in part due to the decline in efficacy.
in neurocognitive function seen in patients treated with WBRT. Fatigue, somnolence, learning, and memory impairments, which often occur with WBRT, are less frequent with the use of stereotactic radiosurgery (SRS).26 To study the treatment effects of WBRT and SRS on neurocognitive function, validated, objective psychometric tests are often used and include Hopkins Verbal Learning Test, Controlled Oral Word Association, Grooved Pegboard Test, and Trail Making A and B tests. These are often performed at baseline and followed over time. In a study that randomized 213 patients to either WBRT plus SRS or SRS alone found at 3 months greater cognitive deterioration and decreased quality of life in patients treated with the WBRT plus SRS. For long-term survivors, the difference in cognitive deterioration was also seen at 12 months.26

One method of minimizing the neurotoxicity of WBRT is the concurrent treatment with N-methyl-D-aspartate glutamate receptor blocker memantine. Radiation to the brain is known to cause overexcitation of the brain, altering the NMDA to GABA receptor ratio, at times resulting in neuronal cell death.27 Memantine was shown to decrease time to cognitive decline and increase executive function, processing speed and delayed recognition.28 This has led the congress of neurological surgeons to recommend memantine for 6 months after WBRT.29 Another method currently being investigated to minimize the neurotoxicity has been hippocampus-sparing WBRT. Data from a phase III trial comparing hippocampal-avoidance WBRT plus memantine to WBRT plus memantine alone were recently published. The authors found that even with memantine, hippocampal avoidance added a significant ability to preserve neurocognitive function at both 4 and 6 months.30,31

WBRT has traditionally played a significant role in the management of small-cell lung cancer (SCLC). Earlier studies demonstrated an overall survival benefit from prophylactic cranial irradiation (PCI) in patients with limited but stable extracranial disease.32,33 In a meta-analysis of 7 trials of 987 patients published in 1999 comparing PCI versus observation with a positive response to initial treatment, those receiving PCI had an improvement in survival at 3 years from 15.3% to 20.7% \( (P = .01) \).32 However, in a recent phase III randomized trial in Japan, the median survival for patients receiving PCI was worse than those with observational MRIs. The median survivals were 11.6 months and 13.7 months, respectively, and this trended toward significance (hazard ratio [HR] 1.27, \( P = .094 \)).34 This new data has brought into question the efficacy of PCI for patients with SCLC.

Stereotactic Radiosurgery

SRS, in contrast to WBRT, involves the precise focusing of radiation from multiple angles to provide a confined area of high-dose radiation. This decreases the dose of radiation reaching healthy tissue and allows avoidance of radiation-sensitive tissue like the optic nerve. SRS plus WBRT was initially shown to improve intracranial control rates as well as improve overall survival.35 However, multiple follow-up studies failed to replicate the overall survival advantage.26,36–38 Based on this data, the US and European guidelines recommend against the addition of WBRT to SRS for patients with less than 4 brain metastases.39,40

Advances in radiosurgery technology have made it possible to treat tens of brain metastases if desired. In a Japanese prospective observational study following almost 1200 patients treated with SRS alone, they found no difference in overall survival between patients with 2–4 versus 5–10 brain metastases (HR 0.97, \( P = .78 \); \( P < .001 \)). Two phase III prospective clinical trials are attempting to provide level 1 evidence for the efficacy of SRS versus WBRT for patients with 4 or more brain metastases (NCT01592968 and NCT02353000).

Postoperative WBRT has been considered standard of care after resection of a single metastasis.23,41 However, with the increased concern of WBRT-associated neurocognitive decline, the role of SRS in these patients was investigated. In a phase III trial comparing SRS to WBRT in the postoperative setting, the cognitive-deterioration-free survival was longer in patients assigned to the SRS group (HR 0.47, \( P < .0001 \)). The cognitive deterioration at 6 months was less frequent in the SRS group (52% vs 85%, \( P < .00031 \)). There was no statistical difference in overall survival.42

In order to determine if SRS was necessary in the postoperative setting, a study was done to compare SRS to the resection cavity and observation with SRS performed only to remaining intact brain metastases. The authors found that the 1-year local control rate was 43% in the observation group and 72% in the SRS group (\( P = .015 \)).42

Additionally, postoperative SRS is associated with increased rates of leptomeningeal disease, especially in the posterior fossa and in breast cancer, compared to postoperative WBRT.43–45 Due to these risks some are investigating the use of preoperative SRS, which has shown to have similar rates of development of leptomeningeal disease compared to WBRT.46,47 However, the data for its efficacy in this setting are limited to retrospective reports.44 Combined, these results establish SRS as an effective adjuvant therapy to surgical resection.

Another advance in the area of radiotherapy is hypofractionated SRS, which typically includes 3–5 treatments at a decreased dose. This decreases toxicity around important structures like the brainstem and optic nerve. This strategy also led to low levels of radiation necrosis and improves local control after fractionated stereotactic radiation therapy for brain metastases.48–52 Also, because SRS alone does not treat microscopic disease, while WBRT is thought to, patients have higher rates of both local and distant recurrence of brain metastases when compared to WBRT plus SRS.53 A meta-analysis including tumors from multiple primaries with 1–4 intracranial lesions calculated an HR for local control of 2.61 \( (P = .015) \) and 2.15 \( (P < .0001) \) for distant brain control favoring WBRT and SRS. However, no difference in overall survival was observed (HR 0.98, \( P = .88 \)).53 It has been shown that distant failure after upfront SRS is correlated with an increasing number of brain metastases, lowest SRS dose, and melanoma histology.54 Repeat courses of SRS in these patients can allow patients to maintain neurocognitive function and their quality of life.55,56 Finally, there is great interest in the coordination of radiation therapy and immunotherapy and preliminary evidence suggests concurrent therapy may increase the intracranial efficacy.57
Surgery

Neurosurgical resection can be useful in a selected patient population; however, due to the potential comorbidities, surgery is not recommended for everyone. Surgery can be helpful for tissue diagnosis, cerebral decompression, reducing mass effect, and vasogenic edema. With the advent of stereotactic neurological techniques, minimally invasive surgical resection is now possible. From a therapeutic perspective, adjuvant radiotherapy is always necessary to provide any survival benefit. Currently, the European Association of Neuro-oncology (EANO) guidelines recommend surgical resection when the systemic disease is absent or controlled and the KPS is 60 or more. Additionally, surgical resection should be considered for lesions at least 3 cm in diameter, lesions with necrotic appearance and edema/mass effect, posterior fossa lesions associated with hydrocephalus, and lesions located in symptomatic eloquent areas.

In addition to direct therapeutic advantages, histopathological analysis of tissue may be necessary for diagnosis and molecular profiling of the tumor. With the development of genetic sequencing, the long hypothesized difference between the primary tumor and the brain metastases has been confirmed. A recent study performed whole-exome sequencing on 86 matched brain metastases, primary tumors, and normal tissue. The authors found that while tumors shared a common ancestor, they continued to evolve independently. In 53% of cases, the authors found clinically informative alterations in the brain metastases not detected in the primary tumor. Besides, spatially and temporally separated brain metastases were similar but highly divergent from distal extracranial metastases. This knowledge suggests that molecular profiling of surgical biopsies may provide clinical benefit, especially with the further development of immunotherapies and targeted therapies.

Role of Steroids and Anti-Epileptic Drugs

Approximately 20–40% of patients with brain tumors have experienced a seizure episode before or at the time of diagnosis. Another 20–45% will develop seizures at some point during their treatment. These statistics make prophylactic anti-epileptic drugs (AEDs) an attractive treatment option. However, the side effects of AEDs include myelosuppression, cognitive impairment, immunosuppression, and liver dysfunction. Despite numerous studies, there is no evidence for prophylactic AEDs use in seizure-naive patients. This led the Congress of Neurological Surgeons to conclude that prophylactic AEDs are not indicated in seizure-naive patients with metastatic brain tumors preoperatively, intraoperatively, or postoperatively. It is important to note that AEDs are recommended in all patients who have experienced a seizure.

Corticosteroids are prescribed for brain metastases to control mass effect and minimize neurological symptoms. Recent guidelines from the Congress of Neurological Surgeons outline the current recommendations for the appropriate setting and the choice of steroid. Dexamethasone is the drug of choice and should always be tapered as quickly as clinically tolerated. In patients with mild symptoms, temporary steroids are recommended for symptomatic relief related to intracranial pressure and edema with a dose starting at 4–8 mg/day of dexamethasone. In patients with moderate to severe symptoms, doses as high as 16 mg/day can be considered.

Lung Cancer

Lung cancer accounts for the greatest proportion of brain metastases and portends a dismal prognosis. Brain metastases can arise from both NSCLC and SCLC. Until recently, surgery and WBRT or SRS were used to treat NSCLC brain metastases. Due to the advances in the understanding of the biology of NSCLC brain metastasis, there is an increasing role of targeted drugs and immunotherapy in the treatment of these (Table 2).

The identification of targetable genetic alterations has led to exciting new therapies for NSCLC. The Lung Cancer Mutation Consortium found that targetable oncogenic drivers have been identified in 64% of patients with NSCLC adenocarcinoma. In addition, oncogenic driver mutations can be identified in up to 80% of squamous NSCLC. However, most of these mutations do not have currently approved therapy. The most recent NSCLC guidelines published by the National Comprehensive Cancer Network (NCCN), 2019 version 4, recommend that the 9 genes related to targeted therapy that should be tested include EGFR, KRAS, HER2, ALK, ROS1, MET, BRAF, RET, and NTRK. As mentioned above, recent studies have highlighted genetic evolution from the primary tumor to the brain metastases, suggesting that additional and/or alternative mutation may be driving intracranial progression. Currently, however, retesting the genetic profile of brain metastases is not standard of care.

Epidermal Growth Factor Receptor

Due to the identification of epidermal growth factor receptor (EGFR) overexpression in NSCLC, there was great excitement around EGFR inhibitors in the early 2000s. However, early unselected clinical trials demonstrated limited clinical efficacy. It was not until 3 papers published in 2004 demonstrated that activating mutations in the EGFR gene were required for sensitivity to gefitinib and erlotinib, first-generation EGFR tyrosine kinase inhibitors (TKIs). EGFR mutations were found to occur at higher rates in never-smokers, and the rate of EGFR mutation patients is highest in the Asian population. The initial retrospective data on the intracranial efficacy in patients harboring EGFR mutations reported intracranial response rates ranging from 42% to 82%. The first prospective data on intracranial efficacy compared responses to EGFR TKIs in patients with or without
EGFR mutations. A phase II study in China found that in patients with asymptomatic brain metastases, EGFR mutations led to a significantly increased overall survival compared to wild-type patients (37.5 months vs 18.4 months, \( P = .02 \)).\(^{79}\) Another phase II trial of the first-generation TKI gefitinib, where all patients had an EGFR mutation and untreated brain metastases, the response rate was 87.8% with an overall survival of 21.9 months.

Unfortunately, the response duration of first-generation EGFR-TKIs is often limited due to secondary mutations, primarily threonine–methionine substitution on codon 790 (T790M).\(^{79,80}\)

### Table 2  Significant Trials in Lung Cancer Brain Metastases

| Clinical Trial Number and Reference | Number of Patients | Phase | Drug | Brain Metastases Patient Selection | Response Data | Survival Data |
|------------------------------------|--------------------|-------|------|-----------------------------------|---------------|---------------|
| UMIN000001755\(^{34}\) | 224 | III | Prophylactic cranial irradiation vs observation in small-cell lung cancer with no brain metastases | No brain metastases at baseline | NA | Median OS 11.6 months vs 13.7 months (HR 1.27, \( P = .094 \)) |
| Iuchi et al.\(^{142}\) | 41 | II | Gefitinib for adenocarcinoma NSCLC with EGFR mutation | Patients with symptomatic and asymptomatic brain metastases, no radiotherapy | 87.8% response rate | Median PFS 14.5 months and median OS 21.9 months. Exon 19 deletions compared to L858R mutation were associated with better outcomes (OS \( P = .025 \)) |
| NCT02296125\(^{92}\) | 556 | III | Osimertinib vs first-generation EGFR-TKI | Only patients with stable asymptomatic brain metastases included | 6% of patients had CNS progression in the osimertinib group compared to 15% in the standard EGFR-TKI group | Osimertinib significantly increased PFS compared to first-generation TKIs (HR 0.46; 95% CI 0.37–0.57) |
| NCT01154140\(^{87}\) | 79 | III | Crizotinib vs pemetrexed plus cisplatin or carboplatin | Only patients with stable asymptomatic brain metastases included | Intracranial disease control rate was significantly higher with crizotinib at 12 weeks (85% vs 45%; \( P < .001 \)) and 24 weeks (56% vs 25%, \( P = .006 \)) | PFS was longer in crizotinib group (HR 0.40, \( P < .001 \)) |
| NCT02075840\(^{95}\) | 303 | III | Alectinib vs crizotinib in ALK-positive NSCLC | Only patients with stable asymptomatic brain metastases included. CNS progression could receive local therapy if isolated asymptomatic CNS progression occurred | 12% of patients in alectinib group had CNS progression vs 45% in crizotinib group (HR 0.16, \( P < .001 \)). CNS complete response was significantly more likely in the alectinib group compared to the crizotinib group (45% vs 9%, \( P < .001 \)) | PFS was longer in the alectinib group (HR 0.47, \( P < .001 \)) |
| NCT01970865\(^{96}\) | 276 | II | Lorlatinib | Only patients with stable asymptomatic brain metastases included | In patients with at least one prior ALK inhibitor, 51 of 81 patients had an intracranial response (63%; 95% CI 51.5–72.4) | NA |
| NCT02578680 | 108 | III | Pemetrexed and platinum-based drug plus pembrolizumab or placebo in patients without EGFR or ALK mutations | Only patients with stable asymptomatic brain metastases included | NA | Pembrolizumab patients had significantly longer OS (HR 0.36, 95% CI 0.20–0.62) and PFS (HR 0.42, 95% CI 0.26–0.68) |
The second-generation EGFR TKI afatinib has also shown intracranial activity. In the LUX-Lung 3 trial, the median time to CNS progression was longer in the afatinib group compared to the chemotherapy group (15.2 months [95% CI 7.7–29.0] vs 5.7 months [95% CI 2.6–8.2]). Additionally, the LUX-Lung 6 trial also demonstrated increased time to CNS progression group (15.2 months [95% CI 3.8–23.7] vs 7.3 months [95% CI 3.7–10.9]). A combined analysis demonstrated a significantly prolonged progression-free survival (PFS) (8.2 vs 5.4 months; HR 0.50, P = .0297).

The third-generation EGFR TKI osimertinib was developed to be effective against the T790M mutation, which is frequently identified after treatment with first-generation TKIs. In a trial for first-line treatment of EGFR-mutated NSCLC comparing osimertinib to first-generation EGFR TKIs, 6% of patients had CNS progression in the osimertinib group compared to 15% in the standard EGFR-TKI group. In addition, osimertinib significantly increased PFS compared to first-generation TKIs (HR 0.46, 95% CI 0.37–0.57). In a subgroup analysis of a trial comparing osimertinib to pemetrexed plus carboplatin or cisplatin in patients who fail first-generation EGFR TKIs, among the 144 patients with brain metastases, the median PFS was longer in the osimertinib group (8.5 months vs 4.2 months; HR 0.32, 95% CI 0.21–0.49). Together, this data consistently have shown better intracranial activity of osimertinib compared to first-generation EGFR TKIs and cytotoxic chemotherapies and is currently considered as first-line treatment for patients with NSCLC. A recent phase III study compared icotinib alone versus WBRT. This study found a significantly improved intracranial PFS in the icotinib alone group (HR 0.56, P < .014). There was no survival benefit in the icotinib alone arm. This drug is only currently approved in China, but highlights the possibility of improved intracranial control with systemic targeted therapies over traditional local therapies.

**Anaplastic Lymphoma Kinase**

In 2007, the gene anaplastic lymphoma kinase (ALK) was found fused with echinoderm microtubule-associated protein-like 4 (EMLA4) gene in patients with NSCLC. Three to seven percent of patients with NSCLC have ALK translocations, and when treated with platinum-based chemotherapy, there is no difference in overall survival. Patients with ALK translocations also have a higher risk of developing brain metastases. The advent of ALK inhibitors has rapidly improved the prognosis of these patients.

ALK inhibitor trials included prospective tumor genotyping, which lead to more rapid and widespread use of these drugs. In the randomized controlled clinical trial for the first-generation ALK inhibitor, crizotinib, 79 patients with stable brain metastases were enrolled. Those patients treated with crizotinib had significantly higher intracranial disease control at 12 and 24 weeks (12 weeks: 85% vs 45%, P < .001; 24 weeks: 56% vs 25%, P = .006). However, resistance to these ALK inhibitors was common and eventually, intracranial progression was seen in most patients.

Second-generation ALK inhibitors, ceritinib, alectinib, and brigatinib, were the next class of ALK inhibitors that were developed. In a phase II trial of ceritinib, of the 100 patients who had baseline brain metastases, there was a 45% intracranial response rate (95% CI 23.1–68.5%) with an 80% intracranial disease control rate. In phase III study, patients with crizotinib-resistant ALK-rearranged NSCLC were treated with alectinib. Of the 21 patients with baseline brain metastases, 11 had an objective response, 6 of which were complete responses. This led to a phase III trial comparing alectinib versus crizotinib in ALK inhibitor naive patients who found a significant improvement in PFS (HR 0.08, 95% CI 0.01–0.61). Within this study, the HR for intracranial PFS was 0.51 (95% CI 0.16–1.64). In a second phase III trial comparing alectinib to crizotinib, patients treated with alectinib, only 12% had CNS progression compared to 45% of patients treated with crizotinib (HR 0.16, 95% CI 0.10–0.28, P < .001). In addition, CNS complete response was significantly more likely in the alectinib group compared to the crizotinib group (45% vs 9%, P-value <.001). The combination of these trials demonstrates the intracranial efficacy of second-generation ALK inhibitors. The first FDA-approved third-generation ALK inhibitor was lorlatinib. Lorlatinib was designed to penetrate the BBB and has broad ALK mutational coverage. In phase II clinical trial, in patients with at least one prior ALK inhibitor, 51 of 81 patients had an intracranial response leading to a 63% response rate (95% CI 51.5–73.4%). This data led to the accelerated approval of lorlatinib for patients who have progressed on crizotinib and at least one other ALK inhibitor for metastatic disease; or whose disease has progressed on alectinib or ceritinib as the first ALK inhibitor therapy for metastatic disease. Currently, ALK-positive patients and patients with EGFR-mutated lung cancer who have asymptomatic brain metastases may be treated with only targeted therapy and have local therapy omitted until progression.

**Immune Checkpoint Inhibitors**

In addition to targeted therapies, immunotherapies are also rapidly altering the treatment of NSCLC. In particular, the anti-PD-1 antibodies pembrolizumab and nivolumab and the PD-L1 antibody atezolizumab have all shown efficacy in NSCLC. PD-L1 expression within the lung tumor is indicative of survival; however, oftentimes PD-L1 expression in an intracranial lesion is unknown. A study of 73 lung cancer patients with paired samples of the primary tumor and brain metastases evaluated the tumor PD-L1 expression and tumor microenvironment PD-L1 expression. The authors found that in 14% of cases, there was a disagreement between the primary site and the brain metastases in tumor cell PD-L1 expression. Additionally, the authors found disagreement in tumor-infiltrating lymphocytes in 26% of cases. Another study found that 7 of 32 patients with NSCLC had PDL1 expression more than 5% in their tumor. This suggested different expression in the brain metastases,
and the primary tumor is possible. However, routine testing of PD-L1 in brain metastases is currently not the standard of care.

Several retrospective studies have investigated the intracranial efficacy of immunotherapy for NSCLC brain metastases. In an Italian series of 409 patients with asymptomatic brain metastases, the disease control rate was 40%. In a French study of 130 patients with brain metastases, 37% had either stable disease or partial response with an overall survival of 6.6 months. In a phase II study of pembrolizumab in patients with NSCLC brain metastases, 33% of patients had an intracranial response. In the phase III KEYNOTE 189 trial of pembrolizumab plus chemotherapy versus chemotherapy alone the HR for patients with asymptomatic treated CNS metastases, 37% had either stable disease or partial response with an overall survival of 6.6 months. In a follow-up abstract investigating the durability of the response, the authors reported a CNS PFS of 10.7 months with 31% of patients surviving at least 2 years. In the phase III KEYNOTE 189 trial of pembrolizumab plus chemotherapy versus chemotherapy alone the HR for patients with stable brain metastases was 0.36 (95% CI 0.20–0.62), supporting the efficacy of pembrolizumab in patients with brain metastases.

### Breast Cancer

Breast cancer is the second most common cancer leading to brain metastases. Triple-negative breast cancer patients are most at risk for the development of brain metastases, with a median overall survival of fewer than 6 months. Unfortunately, targeted therapies for brain metastases in this population are lacking, and these patients are primarily treated with chemotherapy. Recently, the FDA approved atezolizumab (a PD-L1 inhibitor), a class of drugs that have shown some efficacy in brain metastases from melanoma and NSCLC. However, the phase III clinical trial that led to its approval only included patients with asymptomatic treated CNS metastases. While the number of patients in this subgroup was small, there was no statistical difference in PFS between the atezolizumab plus Nab-Paclitaxel versus the placebo plus Nab-Paclitaxel (HR 0.86, 95% CI 0.50–0.62).

#### Table 3

| Clinical Trial Number and Reference | Number of Patients | Phase | Drug | Brain Metastases Patient Selection | Response Data | Survival Data |
|----------------------------------|--------------------|-------|------|------------------------------------|---------------|---------------|
| NCT00967031 114                  | 45                 | II    | Lapatinib and capecitabine for HER2-positive breast cancer | Trial included patients with symptomatic brain metastases | 65.9% (95% CI 50.1–79.5%) had objective CNS response | Median time to CNS progression 5.5 months. OS was 17 months |
| NCT01494662 117                  | 49                 | II    | Neratinib plus capecitabine for HER2-positive breast cancer | Only patients with stable asymptomatic brain metastases included | 49% (95% CI 32–66%) for lapatinib-naive patients (A) and 33% (95% CI 10–65%) for lapatinib-treated patients (B) | PFS was 5.5 months in cohort A and 3.1 months in cohort B. OS was 13.3 months and 15.1 months, respectively |
| NCT02025192 121                  | 60                 | Ib    | Tucatinib with capecitabine with or without trastuzumab | Only patients with stable asymptomatic brain metastases included | 42% achieved a brain-specific objective response | NA |

#### Human Epidermal Growth Factor Receptor 2

In 20–30% of breast cancers, the human EGFR 2 (HER2) is over-expressed. HER2-directed drugs include trastuzumab, pertuzumab, ado-trastuzumab emtansine, neratinib, tucatinib, and lapatinib. A study investigating 377 women with CNS metastasis from HER2-positive breast cancer found that those with brain metastases were younger and more likely to have a higher disease burden. The median time to CNS progression was 13.3 months and those treated with trastuzumab had a significant improvement in median overall survival (17.5 months vs 3.8 months) and was significant on the multivariable analysis (HR 0.33, P < .001). Two other studies have also demonstrated improved overall survival of trastuzumab in patients with brain metastases.

In a phase II trial investigating the small molecule inhibitor lapatinib with capecitabine in patients with untreated brain metastases, 29 of 45 patients had objective CNS response. A study was done to investigate the ability of lapatinib to prevent brain metastases. In the study, HER2-positive metastatic breast cancer patients were treated with either lapatinib or trastuzumab in combination with capecitabine. This trial was closed early due to poor accrual, but the authors ultimately found that the incidence of CNS metastases as the first site of relapse was 3% for the lapatinib group versus 5% for the trastuzumab group (P = .36).

Neratinib is a small molecule irreversible TKI of EGFR, HER2, and HER4 that was hypothesized to have efficacy against brain metastases. As a monotherapy, the intracranial response rate was only 8%; however, in combination with capecitabine, the response rate was 49%. As a result, the NCCN guidelines include neratinib with capecitabine as an option for the management of HER2-positive breast cancer brain metastases. Additionally, the combination of HER2-directed therapy with SRS has been shown to increase local tumor control.
Tucatinib is another small, selective HER2TKI that results in less diarrhea and skin toxicities. A phase I study which combined tucatinib with trastuzumab reported that the combination led to an intracranial objective response rate of 12%. When tucatinib and trastuzumab were combined with capecitabine, 42% of patients had an intracranial objective response. A phase II trial that includes patients with progressive brain metastases (NCT02614794n) is currently investigating this combination.

Hormone Receptor-Positive Disease

The current guidelines for patients with hormone receptor-positive disease recommend endocrine therapy as first-line treatment. Interestingly, the concentration of tamoxifen and its metabolites can be up to 46-fold higher in the brain tissue compared with serum. Additionally, because aromatase inhibitors work by inhibiting the generation of estrogens in the ovaries (premenopausal women) and peripheral tissue (postmenopausal women), this class of drugs does not require brain penetration in order to reduce the levels of estrogen in the brain. However, the survival data supporting endocrine therapy for the treatment of brain metastases are relatively weak and limited. Whole-exome sequencing of 21 patients with breast cancer found frequent alterations of the CDK and PI3K pathways and that these changes were often unique to brain metastases. As a result, the oral CDK inhibitor abemaciclib was studied in the phase III MONARCH trial and showed significantly prolonged PFS (HR 0.54, P = .000021), but the trial excluded patients with brain metastases. An ongoing clinical trial (NCT02308020) is testing the intracranial efficacy of abemaciclib. Early data from this trial demonstrated an intracranial response in 2 of 23 patients.

Melanoma

Melanoma is the third most frequent of the solid tumors that metastasizes to the brain. Estimates predict that up to 75% of patients with metastatic melanoma will have evidence of CNS involvement at the time of autopsy. The key driver mutations in melanoma involve CDKN2A, BRAF, NRAS, and KIT. Of these, mutations to v-RAF murine sarcoma viral oncogene homology B (BRAF) is present in up to 50% of advanced melanoma patients, the majority resulting from a substitution of valine to glutamate at codon 600 (V600E) or valine to lysine at the same codon (V600K) (Table 4).

BRAF Inhibitors

While patients with brain metastases were excluded from the majority of the initial phase III trial for the approval of BRAF inhibitors, the phase II trial BREAK-MB was the first to specifically investigate the intracranial efficacy. In this study, 172 melanoma patients were treated with oral dabrafenib and the authors found a 39% response rate in patients who had not previously received local treatment and 31% in those who had. In a phase II study of Vemurafenib in 146 patients, the authors found that 18% of patients with previously untreated brain metastases had intracranial response. Unfortunately, the response to BRAF inhibitors is limited to a few months and most patients will have disease recurrence within 12 months.

The tumors often become resistant to the BRAF inhibition through the mutations resulting in the reactivation of the MAPK pathway. In order to counter this, MEK inhibitors are often combined with BRAF inhibitors. In a phase II trial with dabrafenib plus trametinib intracranial response was seen between 44% and 59% of patients depending on previous therapies, suggesting the efficacy of the combination. However, the duration of the intracranial response was relatively short, ranging from 4.5 to 8.3 months. Additional phase II trials are currently underway investigating the efficacy of the combination of these drugs (Vemurafenib plus combinetinib NCT02537600 and NCT03430947, and Dabrafenib plus trametinib NCT02974803) with radiosurgery.

Immune Checkpoint Inhibitors

The most promising shift in melanoma brain metastasis care has been the development of immune checkpoint inhibitors. Immune checkpoint inhibitors demonstrate a more durable response compared to BRAF inhibitors. The anti-CTLA4 monoclonal antibody ipilimumab was the first to demonstrate intracranial efficacy. In a phase II trial, patients were separated into 2 groups, those who were not receiving corticosteroids (cohort A) and those who required corticosteroids for symptomatic control (cohort B). The intracranial disease control rate was 24% in cohort A and 10% in cohort B. More striking was the difference in overall survival between the 2 groups 7 months versus 3.7 months. In another phase II trial of patients with untreated brain metastases treated with pembrolizumab, 26% of patients had an intracranial response, with 48% of patients alive at 24 months.

Even more impressive has been the results of CheckMate-204, a phase II clinical trial that enrolled 90 patients with asymptomatic brain metastases and treated with a combination of nivolumab and ipilimumab. Among the 94 patients treated, the rate of intracranial clinical benefit was 57% with a complete intracranial response of 26%. In a similar phase II trial comparing the combination of ipilimumab and nivolumab versus nivolumab alone. In the combination arm, the intracranial response rate was 46% versus 20% in the nivolumab alone arm. However, overall survival was similar between the groups. Of note, the third arm with symptomatic metastases or leptomeningeal disease had significantly worse outcomes. In patients with symptomatic brain metastases who received at least one dose of both ipilimumab and nivolumab had an intracranial response rate of 16.7%.

While these results strongly suggest the durable intracranial efficacy of combination immunotherapy, they were not powered to determine the difference in overall survival.
A phase III trial currently recruiting patients is powered to investigate differences in survival in melanoma brain metastases (NCT02460068). Another phase II trial is comparing the efficacy of ipilimumab plus nivolumab plus SRS compared to ipilimumab plus nivolumab alone and is designed to determine differences in neurologic specific survival at 12 months (NCT03340129). Finally, the efficacy of pembrolizumab in patients with brain metastases is also under investigation (NCT02886585). In the melanoma arm of this trial between cycles 1 and 2 of pembrolizumab, SRS will be administered.

### Table 4 Significant Trials in Melanoma Brain Metastases

| Clinical Trial Number and Reference | Number of Patients | Phase | Drug | Brain Metastases Patient Selection | Response Data | Survival Data |
|------------------------------------|--------------------|-------|------|-----------------------------------|---------------|--------------|
| McArthur et al.133 | 146 | II | Vemurafenib in patients with BRAFV600 mutations with or without prior BM treatment | Trial included both symptomatic and asymptomatic brain metastases patients | In both groups, 18% had intracranial response | Intracranial PFS was 3.7 months in untreated group and 4 months in the previously treated group. Median OS was 8.9 and 9.6 months, respectively |
| NCT01266967132 | 172 | II | Dabrafenib. Cohort A had no previous local therapy and cohort B had previous local therapy for brain metastases | Only patients with stable asymptomatic brain metastases included | Overall intracranial response was 39.2% in cohort A and 30.8% in cohort B | 6 months overall survival was 61% in both cohorts with V600E and 27% for cohort A and 41% for cohort B in V600K |
| NCT02039947135 | 125 | II | Dabrafenib plus trametinib A: BRAFV600E-positive, no previous treatment for BM B: BRAFV600E-positive, with previous treatment for BM C: BRAFV600D/K/R-positive, asymptomatic BM D: BRAFV600D/E/K/R-positive, symptomatic BM | Trial included both symptomatic and asymptomatic brain metastases patients | Intracranial response rate was 58% in A, 56% in B, 44% in C, and 59% in D | Median OS was 10.8 months for A, 24.3 months for B, 10.1 months for C, and 11.5 months for D |
| NCT00623766136 | 72 | II | Ipilimumab. Cohort A was neurologically asymptomatic not receiving steroids. Cohort B was symptomatic and a stable dose of steroids | Trial included both symptomatic and asymptomatic brain metastases patients | Intracranial disease control rate was 24% in A and 10% in B | Median OS was 7 (95% CI 4.1–10.8) months in A and 3.7 (95% CI 1.6–7.3) months in B |
| NCT02085070137 | 23 | II | Pembrolizumab in asymptomatic patients | Only patients with stable asymptomatic brain metastases included | Intracranial response rate was 26% | Median PFS was 2 months and median OS was 17 months. 11 patients were alive at 24 months |
| NCT02320058 | 94 | II | Nivolumab and ipilimumab in untreated asymptomatic BM | Only patients with stable asymptomatic brain metastases included | Intracranial response rate was 57% with 26% complete response | OS at 6 months was 92.3% and 82.8% at 9 months. Intracranial PFS was 64.2% at 6 months and 59.6% at 9 months |

**Future Directions and Conclusion**

Advances in our ability to identify actionable mutations in patients with brain metastases have enabled the development of more advanced trial designs. The Alliance A071701 trial will build off these advances in patients with brain metastases, primarily from lung and breast primary tumors. In this trial, patients with progressive brain metastases who have tissue (brain or extracranial) available for sequencing will be assigned into 1 of 3 cohorts.
Based on genetic alterations. Actionable alterations in the CDK pathway will be treated with abemaciblib as above. Mutations in the PI3K/AKT/mTOR pathways will be treated with the PI3K inhibitor entrectinib. Finally, patients with ALK/NTRK/ROS1 translocations will be treated with an inhibitor of this pathway, GDC-0084. The primary endpoint in this trial will be the CNS response rate.

In the last decade advancements in our understanding of brain metastases and the development of new therapies have provided a new outlook on brain metastases. Developments in radiation therapies with the increased use of SRS and hippocampal sparing WBRT may limit the neurocognitive decline that has been a staple of radiation treatment for many years. In addition, the presence of the BBB led to the historical viewpoint that systemic therapies played little role in the management of brain metastases. Neurocognitive decline and the patient’s quality of life must always be at the forefront of any therapeutic advancement. The presence of BBB led to the historical viewpoint that systemic therapies played little role in the management of brain metastasis. However, advances in targeted therapies and immune checkpoint inhibitors are providing novel medical therapeutics. Moving forward, the appropriate combination of these novel approaches with focused forms of radiation will be an active form of clinical investigation. The new age of precision medicine will enable clinicians to better estimate a patient’s prognosis and help identify appropriate management options promising future improvement in the management of brain metastases and better prognosis for patients.

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