Neuro-Oncology Advances
2(1), 1–14, 2020 | doi:10.1093/noajnl/vdaa015 | Advance Access date 9 August 2020

Medical management of brain metastases

Adam Lauko, Yasmeen Rauf, and Manmeet S. Ahluwalia

Burkhardt Brain Tumor and Neuro-Oncology Center, Cleveland Clinic, Cleveland, Ohio, USA

Corresponding Author: Manmeet Ahluwalia, MD, FACP, Burkhardt Brain Tumor and Neuro-Oncology Center, Neurological Institute, Cleveland Clinic, 9500 Euclid Ave, S73, Cleveland, OH 44195, USA (ahluwam@ccf.org).

Absrtract

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.[1,2] However, the true incidence is likely higher as autopsy studies have reported metastases in 30–40% of patients with cancer.[3,4] 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.[5] 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.[2] 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.[6–8] 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%.[9,10] 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.[11]

The risk of developing brain metastases also increases with more advanced primary disease.[12] 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.[11] 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.[13] 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.[14] 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.[15] Additional prognostic scores have also been developed and the constant in all of these is the inclusion of KPS.[16,17] Similar GPA scores exist for melanoma, RCC, and breast cancer brain metastases.[18–20] Finally, a nomogram for predicting individual survival probabilities has been developed utilizing the Radiation Therapy Oncology Group (RTOG) database.[21]

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.[22] Additionally, temozolomide has minimal efficacy on the primary tumor, with extracerebral response rates ranging from 3% to 43% depending on the primary tumor.[22]

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.[23,24] 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.[25] This is in part due to the decline

Table 1 Significant Trials in Radiotherapy and Radiosurgery for Brain Metastases

Clinical Trial Number	Number of Patients	Phase	Treatment	Response Data	Survival Data
NCT00377156[26]	213	III	SRS vs SRS plus WBRT	Cognitive deterioration at 3 months: 63.5% vs 91.7% ($P < .001$) Change in quality of life: –1.3 vs –10.9 points ($P = .002$) Time to intracranial failure shorter in SRS alone (HR 3.6, $P < .001$)	Median OS: 10.4 vs 7.4 months (HR 1.02, $P = .92$)
NCT00566852[28]	508	II	WBRT alone vs WBRT plus memantine	Memantine arm had significantly longer to cognitive decline (HR 0.78, $P = .01$)	Median OS: 4.7 vs 5.5 months (HR 1.06, $P = .28$)
NCT02360215[30]	518	III	WBRT plus memantine (WBRT+M) vs hippocampal avoidance plus WBRT+M (HA-WBRT+M)	HA-WBRT+M had lower NCF failure (HR 0.74, $P = .02$). HA-WBRT+M also had lower risk of deterioration of executive function ($P = .01$), encoding ($P = .049$) and consolidation ($P = .0002$)	"Treatment arms did not differ in overall survival or intracranial progression"
NCT00950001[42]	132	III	SRS of resection cavity post surgery vs observation	12 months freedom from local recurrence was 43% vs 72% (HR 0.46, $P = .015$)	No difference in overall survival (HR 1.29, $P = .24$)

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 glutamine 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.[26,35–38] 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 non-inferiority <.0001). 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 < .0001) 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 neurosurgical 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.[39]

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.[58] 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 metastasis were similar but highly divergent from distal extracranial metastases.[58] 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.[59] 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.[60] 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.[61] 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.[62] 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.[63] 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.[64,65] 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*.[66] 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.[58] 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.[67–70] 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).[71–73] 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.[74] The initial retrospective data on the intracranial efficacy in patients harboring EGFR mutations reported intracranial response rates ranging from 42% to 82%.[75–77]

The first prospective data on intracranial efficacy compared responses to EGFR TKIs in patients with or without

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[82]	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 crizotinibat 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 51.5–73.4)	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)

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, $P = .02$).[78] 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]

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]).[81] 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]).[81] 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).[82] 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).[83] 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.[84] 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.[85] 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.[86] 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%, $P = .006$).[87] 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.[88–90] 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.[91] In phase I/II 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.[92] 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).[93,94] 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).[95] 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%).[96] 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.[97–99] 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.[100] 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.[101] 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%.[102] 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.[103] In a phase II study of pembrolizumab in patients with NSCLC brain metastases, 33% of patients had an intracranial response.[104,105] 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.[105] 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.[98]

Breast Cancer

Breast cancer is the second most common cancer leading to brain metastases.[5] 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.[106,107] Unfortunately, targeted therapies for brain metastases in this population are lacking, and these patients are primarily treated with chemotherapy.[108] 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 0.50–1.49) (Table 3).[109]

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.[110] 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.[111] 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.[112,113]

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.[114] 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 ($P = .36$).[115]

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%.[116,117] As a result, the NCCN guidelines include neratinib with capecitabine as an option for the management of *HER2*-positive breast cancer brain metastases.[108] Additionally, the combination of *HER2*-directed therapy with SRS has been shown to increase local tumor control.[118,119]

Table 3 Significant Trials in Breast Cancer Brain Metastases

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-naïve 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

Tucatinib is another small, selective *HER2*TKI that results in less diarrhea and skin toxicities.[120,121] A phase I study which combined tucatinib with trastuzumab reported that the combination led to an intracranial objective response rate of 12%.[122] When tucatinib and trastuzumab were combined with capecitabine, 42% of patients had an intracranial objective response.[121] 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.[123] Interestingly, the concentration of tamoxifen and its metabolites can be up to 46-fold higher in the brain tissue compared with serum.[124] 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.[125,126] 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.[58] 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.[127] 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.[128]

Melanoma

Melanoma is the third most frequent of the solid tumors that metastasizes to the brain.[7] Estimates predict that up to 75% of patients with metastatic melanoma will have evidence of CNS involvement at the time of autopsy.[129] The key driver mutations in melanoma involve *CDKN2A*, *BRAF*, *NRAS*, and *KIT*.[130] 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).[131,132]

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.[132] 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.[133] Unfortunately, the response to *BRAF* inhibitors is limited to a few months and most patients will have disease recurrence within 12 months.[134]

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.[135] Additional phase II trials are currently underway investigating the efficacy of the combination of these drugs (Vemurafenib plus combimetinib 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.[136] 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.[137]

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%.[138] 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.[139] 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%.[140]

While these results strongly suggest the durable intracranial efficacy of combination immunotherapy, they were not powered to determine the difference in overall survival.

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
NCT01266967[132]	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
NCT02039947[135]	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
NCT00623766[136]	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
NCT02085070[137]	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

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).[141] 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.

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 abemaciclib 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.[142]

Funding and Conflict of Interest Statement

Conflict of Interest for Manmeet Ahluwalia includes receipt of grants/research supports: Astrazeneca, Abbvie, BMS, Bayer, Incyte, Pharmacyclics, Novocure, Merck. Receipt of honoraria or consultation fees: Elsevier, Wiley, Astrazeneca, Abbvie, VBI Vaccines, Flatiron, Varian Medical Systems, Prime Education, Bayer, Karyopharm, Tocagen, Forma therapeutics. Stock shareholder: Doctible, Mimivax. Other authors have no conflict to report.

References

1. Tabouret E, Chinot O, Metellus P, Tallet A, Viens P, Gonçalves A. Recent trends in epidemiology of brain metastases: an overview. *Anticancer Res.* 2012;32(11):4655–4662.
2. Hall WA, Djalilian HR, Nussbaum ES, Cho KH. Long-term survival with metastatic cancer to the brain. *Med Oncol.* 2000;17(4):279–286.
3. Percy AK, Elveback LR, Okazaki H, Kurland LT. Neoplasms of the central nervous system. Epidemiologic considerations. *Neurology.* 1972;22(1):40–48.
4. Tsukada Y, Fouad A, Pickren JW, Lane WW. Central nervous system metastasis from breast carcinoma. Autopsy study. *Cancer.* 1983;52(12):2349–2354.
5. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. *CA Cancer J Clin.* 2017;67(1):7–30.
6. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. *Curr Oncol Rep.* 2012;14(1):48–54.
7. Barnholtz-Sloan JS, Sloan AE, Davis FG, Vigneau FD, Lai P, Sawaya RE. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the metropolitan Detroit cancer surveillance system. *J Clin Oncol.* 2004;22(14):2865–2872.
8. Berghoff AS, Schur S, Füreder LM, et al. Descriptive statistical analysis of a real life cohort of 2419 patients with brain metastases of solid cancers. *ESMO Open.* 2016;1(2):e000024.
9. Sørensen JB, Hansen HH, Hansen M, Dombernowsky P. Brain metastases in adenocarcinoma of the lung: frequency, risk groups, and prognosis. *J Clin Oncol.* 1988;6(9):1474–1480.
10. Toyokawa G, Seto T, Takenoyama M, Ichinose Y. Insights into brain metastasis in patients with ALK+ lung cancer: is the brain truly a sanctuary? *Cancer Metastasis Rev.* 2015;34(4):797–805.
11. Martin AM, Cagney DN, Catalano PJ, et al. Brain metastases in newly diagnosed breast cancer: a population-based study. *JAMA Oncol.* 2017;3(8):1069–1077.
12. Steeg PS, Camphausen KA, Smith QR. Brain metastases as preventive and therapeutic targets. *Nat Rev Cancer.* 2011;11(5):352–363.
13. Hung MH, Liu CY, Shiau CY, et al. Effect of age and biological subtype on the risk and timing of brain metastasis in breast cancer patients. *PLoS One.* 2014;9(2):e89389.
14. Sperduto PW, Berkey B, Gaspar LE, Mehta M, Curran W. A new prognostic index and comparison to three other indices for patients with brain metastases: an analysis of 1,960 patients in the RTOG database. *Int J Radiat Oncol Biol Phys.* 2008;70(2):510–514.
15. Sperduto PW, Yang TJ, Beal K, et al. Estimating survival in patients with lung cancer and brain metastases: an update of the graded prognostic assessment for lung cancer using molecular markers (Lung-molGPA). *JAMA Oncol.* 2017;3(6):827–831.
16. Lorenzoni J, Devriendt D, Massager N, et al. Radiosurgery for treatment of brain metastases: estimation of patient eligibility using three stratification systems. *Int J Radiat Oncol Biol Phys.* 2004;60(1):218–224.
17. Weltman E, Salvajoli JV, Brandt RA, et al. Radiosurgery for brain metastases: a score index for predicting prognosis. *Int J Radiat Oncol Biol Phys.* 2000;46(5):1155–1161.
18. Sperduto PW, Jiang W, Brown PD, et al. The prognostic value of BRAF, C-KIT, and NRAS mutations in melanoma patients with brain metastases. *Int J Radiat Oncol Biol Phys.* 2017;98(5):1069–1077.
19. Sperduto PW, Kased N, Roberge D, et al. Effect of tumor subtype on survival and the graded prognostic assessment for patients with breast cancer and brain metastases. *Int J Radiat Oncol Biol Phys.* 2012;82(5):2111–2117.
20. Sperduto PW, Deegan BJ, Li J, et al. Estimating survival for renal cell carcinoma patients with brain metastases: an update of the Renal Graded Prognostic Assessment tool. *Neuro Oncol.* 2018;20(12):1652–1660.
21. Barnholtz-Sloan JS, Yu C, Sloan AE, et al. A nomogram for individualized estimation of survival among patients with brain metastasis. *Neuro Oncol.* 2012;14(7):910–918.
22. Zhu W, Zhou L, Qian JQ, Qiu TZ, Shu YQ, Liu P. Temozolomide for treatment of brain metastases: a review of 21 clinical trials. *World J Clin Oncol.* 2014;5(1):19–27.
23. Patchell RA, Tibbs PA, Walsh JW, et al. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med.* 1990;322(8):494–500.
24. Vecht CJ, Haaxma-Reiche H, Noordijk EM, et al. Treatment of single brain metastasis: radiotherapy alone or combined with neurosurgery? *Ann Neurol.* 1993;33(6):583–590.

25. Kann BH, Park HS, Johnson SB, Chiang VL, Yu JB. Radiosurgery for brain metastases: changing practice patterns and disparities in the United States. *J Natl Compr Canc Netw.* 2017;15(12):1494–1502.
26. Brown PD, Jaeckle K, Ballman KV, et al. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA.* 2016;316(4):401–409.
27. Dye NB, Gondi V, Mehta MP. Strategies for preservation of memory function in patients with brain metastases. *Chin Clin Oncol.* 2015;4(2):24.
28. Brown PD, Pugh S, Laack NN, et al.; Radiation Therapy Oncology Group (RTOG). Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol.* 2013;15(10):1429–1437.
29. Gaspar LE, Prabhu RS, Hdeib A, et al. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of whole brain radiation therapy in adults with newly diagnosed metastatic brain tumors. *Neurosurgery.* 2019;84(3):E159–E162.
30. Gondi V, Deshmukh S, Brown PD, et al. NRG oncology CC001: a phase III trial of hippocampal avoidance (HA) in addition to whole-brain radiotherapy (WBRT) plus memantine to preserve neurocognitive function (NCF) in patients with brain metastases (BM). *J Clin Oncol.* 2019;37(15_suppl):2009–2009.
31. Gondi V, Deshmukh S, Brown PD, et al. Preservation of neurocognitive function with conformal avoidance of the hippocampus during wholebrain radiotherapy for brain metastases: preliminary results of phase III trial NRG Oncology CC001 [Abstract]. *2018 Annual Meeting ASTRO Abstract LBA9*; October 2018.
32. Aupérin A, Arriagada R, Pignon JP, et al. Prophylactic cranial irradiation for patients with small-cell lung cancer in complete remission. prophylactic cranial irradiation overview collaborative group. *N Engl J Med.* 1999;341(7):476–484.
33. Slotman B, Faivre-Finn C, Kramer G, et al.; EORTC Radiation Oncology Group and Lung Cancer Group. Prophylactic cranial irradiation in extensive small-cell lung cancer. *N Engl J Med.* 2007;357(7):664–672.
34. Takahashi T, Yamanaka T, Seto T, et al. Prophylactic cranial irradiation versus observation in patients with extensive-disease small-cell lung cancer: a multicentre, randomised, open-label, phase 3 trial. *Lancet Oncol.* 2017;18(5):663–671.
35. Andrews DW, Scott CB, Sperduto PW, et al. Whole brain radiation therapy with or without stereotactic radiosurgery boost for patients with one to three brain metastases: phase III results of the RTOG 9508 randomised trial. *Lancet.* 2004;363(9422):1665–1672.
36. Aoyama H, Shirato H, Tago M, et al. Stereotactic radiosurgery plus whole-brain radiation therapy vs stereotactic radiosurgery alone for treatment of brain metastases: a randomized controlled trial. *JAMA.* 2006;295(21):2483–2491.
37. Chang EL, Wefel JS, Hess KR, et al. Neurocognition in patients with brain metastases treated with radiosurgery or radiosurgery plus whole-brain irradiation: a randomised controlled trial. *Lancet Oncol.* 2009;10(11):1037–1044.
38. Kocher M, Soffietti R, Abacioglu U, et al. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol.* 2011;29(2):134–141.
39. Soffietti R, Abacioglu U, Baumert B, et al. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). *Neuro Oncol.* 2017;19(2):162–174.
40. 2014 Choosing Wisely List—American Society for Radiation Oncology (ASTRO)—American Society for Radiation Oncology (ASTRO). ASTRO. https://www.astro.org/Patient-Care-and-Research/Patient-Education/2014-Choosing-Wisely-List. Accessed June 8, 2019.
41. Patchell RA, Tibbs PA, Regine WF, et al. Postoperative radiotherapy in the treatment of single metastases to the brain: a randomized trial. *JAMA.* 1998;280(17):1485–1489.
42. Mahajan A, Ahmed S, McAleer MF, et al. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol.* 2017;18(8):1040–1048.
43. Atalar B, Modlin LA, Choi CY, et al. Risk of leptomeningeal disease in patients treated with stereotactic radiosurgery targeting the postoperative resection cavity for brain metastases. *Int J Radiat Oncol Biol Phys.* 2013;87(4):713–718.
44. Routman DM, Yan E, Vora S, et al. Preoperative stereotactic radiosurgery for brain metastases. *Front Neurol.* 2018;9:959.
45. Suki D, Abouassi H, Patel AJ, Sawaya R, Weinberg JS, Groves MD. Comparative risk of leptomeningeal disease after resection or stereotactic radiosurgery for solid tumor metastasis to the posterior fossa. *J Neurosurg.* 2008;108(2):248–257.
46. Patel KR, Burri SH, Boselli D, et al. Comparing pre-operative stereotactic radiosurgery (SRS) to post-operative whole brain radiation therapy (WBRT) for resectable brain metastases: a multi-institutional analysis. *J Neurooncol.* 2017;131(3):611–618.
47. Patel KR, Burri SH, Asher AL, et al. Comparing preoperative with postoperative stereotactic radiosurgery for resectable brain metastases: a multi-institutional analysis. *Neurosurgery.* 2016;79(2):279–285.
48. Marcrom SR, McDonald AM, Thompson JW, et al. Fractionated stereotactic radiation therapy for intact brain metastases. *Adv Radiat Oncol.* 2017;2(4):564–571.
49. Minniti G, D'Angelillo RM, Scaringi C, et al. Fractionated stereotactic radiosurgery for patients with brain metastases. *J Neurooncol.* 2014;117(2):295–301.
50. Angelov L, Mohammadi AM, Bennett EE, et al. Impact of 2-staged stereotactic radiosurgery for treatment of brain metastases ≥ 2 cm. *J Neurosurg.* 2018;129(2):366–382.
51. Yomo S, Hayashi M, Nicholson C. A prospective pilot study of two-session Gamma Knife surgery for large metastatic brain tumors. *J Neurooncol.* 2012;109(1):159–165.
52. Higuchi Y, Serizawa T, Nagano O, et al. Three-staged stereotactic radiotherapy without whole brain irradiation for large metastatic brain tumors. *Int J Radiat Oncol Biol Phys.* 2009;74(5):1543–1548.
53. Tsao MN, Lloyd N, Wong RKS, et al. Whole brain radiotherapy for the treatment of newly diagnosed multiple brain metastases. *Cochrane Database Syst Rev.* 2012;(4):CD003869.
54. McTyre E, Ayala-Peacock D, Contessa J, et al. Multi-institutional competing risks analysis of distant brain failure and salvage patterns after upfront radiosurgery without whole brain radiotherapy for brain metastasis. *Ann Oncol.* 2018;29(2):497–503.
55. Shen CJ, Rigamonti D, Redmond KJ, Kummerlowe MN, Lim M, Kleinberg LR. The strategy of repeat stereotactic radiosurgery without whole brain radiation treatment for new brain metastases: outcomes and implications for follow-up monitoring. *Pract Radiat Oncol.* 2016;6(6):409–416.
56. Kotecha R, Damico N, Miller JA, et al. Three or more courses of stereotactic radiosurgery for patients with multiply recurrent brain metastases. *Neurosurgery.* 2017;80(6):871–879.
57. Kotecha R, Kim JM, Miller JA, et al. The impact of sequencing PD-1/PD-L1 inhibitors and stereotactic radiosurgery for patients with brain metastasis. *Neuro Oncol.* 2019;21(8):1060–1068.
58. Brastianos PK, Carter SL, Santagata S, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov.* 2015;5(11):1164–1177.
59. Glantz MJ, Cole BF, Forsyth PA, et al. Practice parameter: anticonvulsant prophylaxis in patients with newly diagnosed brain tumors. Report of the

quality standards subcommittee of the American Academy of Neurology. *Neurology.* 2000;54(10):1886–1893.
60. Chen CC, Rennert RC, Olson JJ. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of prophylactic anticonvulsants in the treatment of adults with metastatic brain tumors. *Neurosurgery.* 2019;84(3):E195–E197.
61. Ryken TC, Kuo JS, Prabhu RS, Sherman JH, Kalkanis SN, Olson JJ. Congress of neurological surgeons systematic review and evidence-based guidelines on the role of steroids in the treatment of adults with metastatic brain tumors. *Neurosurgery.* 2019;84(3):E189–E191.
62. Noone AM, Howlader N, Krapcho M, Miller D, Brest A, Yu M, Ruhl J, Tatalovich Z, Mariotto A, Lewis DR, Chen HS, Feuer EJ, Cronin KA (eds). *SEER Cancer Statistics Review, 1975–2015.* National Cancer Institute. Bethesda, MD, https://seer.cancer.gov/csr/1975_2015/, based on November 2017 SEER data submission, posted to the SEER web site, April 2018.
63. Kris MG, Johnson BE, Berry LD, et al. Using multiplexed assays of oncogenic drivers in lung cancers to select targeted drugs. *JAMA.* 2014;311(19):1998–2006.
64. Alamgeer M, Ganju V, Watkins DN. Novel therapeutic targets in non-small cell lung cancer. *Curr Opin Pharmacol.* 2013;13(3):394–401.
65. Savas P, Hughes B, Solomon B. Targeted therapy in lung cancer: IPASS and beyond, keeping abreast of the explosion of targeted therapies for lung cancer. *J Thorac Dis.* 2013;5(suppl 5):S579–S592.
66. Dong J, Li B, Lin D, Zhou Q, Huang D. Advances in targeted therapy and immunotherapy for non-small cell lung cancer based on accurate molecular typing. *Front Pharmacol.* 2019;10(230):230.
67. Giaccone G, Herbst RS, Manegold C, et al. Gefitinib in combination with gemcitabine and cisplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 1. *J Clin Oncol.* 2004;22(5):777–784.
68. Herbst RS, Giaccone G, Schiller JH, et al. Gefitinib in combination with paclitaxel and carboplatin in advanced non-small-cell lung cancer: a phase III trial–INTACT 2. *J Clin Oncol.* 2004;22(5):785–794.
69. Herbst RS, Prager D, Hermann R, et al.; TRIBUTE Investigator Group. TRIBUTE: a phase III trial of erlotinib hydrochloride (OSI-774) combined with carboplatin and paclitaxel chemotherapy in advanced non-small-cell lung cancer. *J Clin Oncol.* 2005;23(25):5892–5899.
70. Gatzemeier U, Pluzanska A, Szczesna A, et al. Phase III study of erlotinib in combination with cisplatin and gemcitabine in advanced non-small-cell lung cancer: the Tarceva Lung Cancer Investigation Trial. *J Clin Oncol.* 2007;25(12):1545–1552.
71. Paez JG, Jänne PA, Lee JC, et al. EGFR mutations in lung cancer: correlation with clinical response to gefitinib therapy. *Science.* 2004;304(5676):1497–1500.
72. Lynch TJ, Bell DW, Sordella R, et al. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med.* 2004;350(21):2129–2139.
73. Pao W, Miller V, Zakowski M, et al. EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. *Proc Natl Acad Sci U S A.* 2004;101(36):13306–13311.
74. Midha A, Dearden S, McCormack R. EGFR mutation incidence in non-small-cell lung cancer of adenocarcinoma histology: a systematic review and global map by ethnicity (mutMapII). *Am J Cancer Res.* 2015;5(9):2892–2911.
75. Hotta K, Kiura K, Ueoka H, et al. Effect of gefitinib ('Iressa', ZD1839) on brain metastases in patients with advanced non-small-cell lung cancer. *Lung Cancer.* 2004;46(2):255–261.
76. Kim JE, Lee DH, Choi Y, et al. Epidermal growth factor receptor tyrosine kinase inhibitors as a first-line therapy for never-smokers with adenocarcinoma of the lung having asymptomatic synchronous brain metastasis. *Lung Cancer.* 2009;65(3):351–354.
77. Porta R, Sánchez-Torres JM, Paz-Ares L, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. *Eur Respir J.* 2011;37(3):624–631.
78. Wu YL, Zhou C, Cheng Y, et al. Erlotinib as second-line treatment in patients with advanced non-small-cell lung cancer and asymptomatic brain metastases: a phase II study (CTONG-0803). *Ann Oncol.* 2013;24(4):993–999.
79. Kobayashi S, Boggon TJ, Dayaram T, et al. EGFR mutation and resistance of non-small-cell lung cancer to gefitinib. *N Engl J Med.* 2005;352(8):786–792.
80. Sequist LV, Waltman BA, Dias-Santagata D, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. *Sci Transl Med.* 2011;3(75):75ra26.
81. Schuler M, Wu YL, Hirsh V, et al. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thorac Oncol.* 2016;11(3):380–390.
82. Soria JC, Ohe Y, Vansteenkiste J, et al.; FLAURA Investigators. Osimertinib in untreated EGFR-mutated advanced non-small-cell lung cancer. *N Engl J Med.* 2018;378(2):113–125.
83. Mok TS, Wu YL, Papadimitrakopoulou VA. Osimertinib in EGFR T790M-positive lung cancer. *N Engl J Med.* 2017;376(20):1993–1994.
84. Yang JJ, Zhou C, Huang Y, et al. Icotinib versus whole-brain irradiation in patients with EGFR-mutant non-small-cell lung cancer and multiple brain metastases (BRAIN): a multicentre, phase 3, open-label, parallel, randomised controlled trial. *Lancet Respir Med.* 2017;5(9):707–716.
85. Soda M, Choi YL, Enomoto M, et al. Identification of the transforming EML4-ALK fusion gene in non-small-cell lung cancer. *Nature.* 2007;448(7153):561–566.
86. Petrelli F, Lazzari C, Ardito R, et al. Efficacy of ALK inhibitors on NSCLC brain metastases: a systematic review and pooled analysis of 21 studies. *PLoS One.* 2018;13(7):e0201425.
87. Solomon BJ, Cappuzzo F, Felip E, et al. intracranial efficacy of crizotinib versus chemotherapy in patients with advanced ALK-positive non-small-cell lung cancer: results from PROFILE 1014. *J Clin Oncol.* 2016;34(24):2858–2865.
88. Shaw AT, Kim DW, Nakagawa K, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. *N Engl J Med.* 2013;368(25):2385–2394.
89. Shaw AT, Gandhi L, Gadgeel S, et al.; Study Investigators. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single-group, multicentre, phase 2 trial. *Lancet Oncol.* 2016;17(2):234–242.
90. Kim DW, Tiseo M, Ahn MJ, et al. Brigatinib in patients with crizotinib-refractory anaplastic lymphoma kinase-positive non-small-cell lung cancer: a randomized, multicenter phase II trial. *J Clin Oncol.* 2017;35(22):2490–2498.
91. Crinò L, Ahn MJ, De Marinis F, et al. Multicenter phase ii study of whole-body and intracranial activity with ceritinib in patients with ALK-rearranged non-small-cell lung cancer previously treated with chemotherapy and crizotinib: results from ASCEND-2. *J Clin Oncol.* 2016;34(24):2866–2873.
92. Gadgeel SM, Gandhi L, Riely GJ, et al. Safety and activity of alectinib against systemic disease and brain metastases in patients with crizotinib-resistant ALK-rearranged non-small-cell lung cancer (AF-002JG): results from the dose-finding portion of a phase ½ study. *Lancet Oncol.* 2014;15(10):1119–1128.
93. Hida T, Nokihara H, Kondo M, et al. Alectinib versus crizotinib in patients with ALK-positive non-small-cell lung cancer (J-ALEX): an open-label, randomised phase 3 trial. *Lancet.* 2017;390(10089):29–39.

94. Nishio M, Nakagawa K, Mitsudomi T, et al. Analysis of central nervous system efficacy in the J-ALEX study of alectinib versus crizotinib in ALK-positive non-small-cell lung cancer. *Lung Cancer*. 2018;121:37–40.
95. Peters S, Camidge DR, Shaw AT, et al.; ALEX Trial Investigators. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med*. 2017;377(9):829–838.
96. Solomon BJ, Besse B, Bauer TM, et al. Lorlatinib in patients with ALK-positive non-small-cell lung cancer: results from a global phase 2 study. *Lancet Oncol*. 2018;19(12):1654–1667.
97. Rittmeyer A, Barlesi F, Waterkamp D, et al.; OAK Study Group. Atezolizumab versus docetaxel in patients with previously treated non-small-cell lung cancer (OAK): a phase 3, open-label, multicentre randomised controlled trial. *Lancet*. 2017;389(10066):255–265.
98. Gandhi L, Rodríguez-Abreu D, Gadgeel S, et al.; KEYNOTE-189 Investigators. Pembrolizumab plus chemotherapy in metastatic non-small-cell lung cancer. *N Engl J Med*. 2018;378(22):2078–2092.
99. Borghaei H, Paz-Ares L, Horn L, et al. Nivolumab versus docetaxel in advanced nonsquamous non-small-cell lung cancer. *N Engl J Med*. 2015;373(17):1627–1639.
100. Mansfield AS, Aubry MC, Moser JC, et al. Temporal and spatial discordance of programmed cell death-ligand 1 expression and lymphocyte tumor infiltration between paired primary lesions and brain metastases in lung cancer. *Ann Oncol*. 2016;27(10):1953–1958.
101. Takamori S, Toyokawa G, Okamoto I, et al. Clinical significance of PD-L1 expression in brain metastases from non-small cell lung cancer. *Anticancer Res*. 2018;38(1):553–557.
102. Crinò L, Bidoli P, Ulivi P, et al. P1.01-053 Italian Nivolumab Expanded Access Programme (EAP): data from patients with advanced non-squamous NSCLC and brain metastases. *J Thorac Oncol*. 2017;12(11):S1915.
103. Molinier O, Audigier-Valette C, Cadranel J, et al. OA 17.05 IFCT-1502 CLINIVO: real-life experience with nivolumab in 600 patients (Pts) with advanced non-small cell lung cancer (NSCLC). *J Thorac Oncol*. 2017;12(11):S1793.
104. Goldberg SB, Gettinger SN, Mahajan A, et al. Pembrolizumab for patients with melanoma or non-small-cell lung cancer and untreated brain metastases: early analysis of a non-randomised, open-label, phase 2 trial. *Lancet Oncol*. 2016;17(7):976–983.
105. Goldberg SB, Gettinger SN, Mahajan A, et al. Durability of brain metastasis response and overall survival in patients with non-small cell lung cancer (NSCLC) treated with pembrolizumab. *J Clin Oncol*. 2018;36(15_suppl):2009–2009.
106. Sperduto PW, Chao ST, Sneed PK, et al. Diagnosis-specific prognostic factors, indexes, and treatment outcomes for patients with newly diagnosed brain metastases: a multi-institutional analysis of 4,259 patients. *Int J Radiat Oncol Biol Phys*. 2010;77(3):655–661.
107. Lin NU, Amiri-Kordestani L, Palmieri D, Liewehr DJ, Steeg PS. CNS metastases in breast cancer: old challenge, new frontiers. *Clin Cancer Res*. 2013;19(23):6404–6418.
108. Leone JP, Lin NU. Systemic therapy of central nervous system metastases of breast cancer. *Curr Oncol Rep*. 2019;21(6):49.
109. Schmid P, Adams S, Rugo HS, et al.; IMpassion130 Trial Investigators. Atezolizumab and nab-paclitaxel in advanced triple-negative breast cancer. *N Engl J Med*. 2018;379(22):2108–2121.
110. Ross JS, Gay LM. Comprehensive genomic sequencing and the molecular profiles of clinically advanced breast cancer. *Pathology*. 2017;49(2):120–132.
111. Brufsky AM, Mayer M, Rugo HS, et al. Central nervous system metastases in patients with HER2-positive metastatic breast cancer: incidence, treatment, and survival in patients from registHER. *Clin Cancer Res*. 2011;17(14):4834–4843.
112. Bartsch R, Rottenfusser A, Wenzel C, et al. Trastuzumab prolongs overall survival in patients with brain metastases from Her2 positive breast cancer. *J Neurooncol*. 2007;85(3):311–317.
113. Yap YS, Cornelio GH, Devi BC, et al. Brain metastases in Asian HER2-positive breast cancer patients: anti-HER2 treatments and their impact on survival. *Br J Cancer*. 2012;107(7):1075–1082.
114. Bachelot T, Romieu G, Campone M, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER2-positive metastatic breast cancer (LANDSCAPE): a single-group phase 2 study. *Lancet Oncol*. 2013;14(1):64–71.
115. Pivot X, Manikhas A, Żurawski B, et al. CEREBEL (EGF111438): a phase III, randomized, open-label study of lapatinib plus capecitabine versus trastuzumab plus capecitabine in patients with human epidermal growth factor receptor 2-positive metastatic breast cancer. *J Clin Oncol*. 2015;33(14):1564–1573.
116. Freedman RA, Gelman RS, Wefel JS, et al. Translational breast cancer research consortium (TBCRC) 022: a phase II trial of neratinib for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol*. 2016;34(9):945–952.
117. Freedman RA, Gelman RS, Anders CK, et al. TBCRC 022: a phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2-positive breast cancer and brain metastases. *J Clin Oncol*. 2019;37(13):1081–1089.
118. Kim JM, Miller JA, Kotecha R, et al. Stereotactic radiosurgery with concurrent HER2-directed therapy is associated with improved objective response for breast cancer brain metastasis. *Neuro Oncol*. 2019;21(5):659–668.
119. Parsai S, Miller JA, Juloori A, et al. Stereotactic radiosurgery with concurrent lapatinib is associated with improved local control for HER2-positive breast cancer brain metastases. *J Neurosurg*. 2019;132(2):503–511.
120. Borges VF, Ferrario C, Aucoin N, et al. Tucatinib combined with ado-trastuzumab emtansine in advanced ERBB2/HER2-positive metastatic breast cancer: a phase 1b clinical trial. *JAMA Oncol*. 2018;4(9):1214–1220.
121. Murthy R, Borges VF, Conlin A, et al. Tucatinib with capecitabine and trastuzumab in advanced HER2-positive metastatic breast cancer with and without brain metastases: a non-randomised, open-label, phase 1b study. *Lancet Oncol*. 2018;19(7):880–888.
122. Metzger O, Barry W, Krop I, et al. Abstract P1-12-04: phase I dose-escalation trial of ONT-380 in combination with trastuzumab in patients (pts) with HER2+ breast cancer brain metastases. *Cancer Res*. 2017;77(4 suppl):P1-12-04–P1-12-04.
123. Rugo HS, Rumble RB, Macrae E, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology guideline. *J Clin Oncol*. 2016;34(25):3069–3103.
124. Lien EA, Wester K, Lønning PE, Solheim E, Ueland PM. Distribution of tamoxifen and metabolites into brain tissue and brain metastases in breast cancer patients. *Br J Cancer*. 1991;63(4):641–645.
125. Goyal S, Puri T, Julka PK, Rath GK. Excellent response to letrozole in brain metastases from breast cancer. *Acta Neurochir (Wien)*. 2008;150(6):613–614; discussion 614.
126. Ito K, Ito T, Okada T, et al. A case of brain metastases from breast cancer that responded to anastrozole monotherapy. *Breast J*. 2009;15(4):435–437.
127. Goetz MP, Toi M, Campone M, et al. MONARCH 3: abemaciclib as initial therapy for advanced breast cancer. *J Clin Oncol*. 2017;35(32):3638–3646.
128. Tolaney SM, Lin NU, Thornton D, et al. Abemaciclib for the treatment of brain metastases (BM) secondary to hormone receptor positive (HR+), HER2 negative breast cancer. *J Clin Oncol*. 2017;35(15_suppl):1019–1019.

129. Davies MA, Liu P, McIntyre S, et al. Prognostic factors for survival in melanoma patients with brain metastases. *Cancer.* 2011;117(8):1687–1696.

130. Hodis E, Watson IR, Kryukov GV, et al. A landscape of driver mutations in melanoma. *Cell.* 2012;150(2):251–263.

131. Berghoff AS, Preusser M. Targeted therapies for melanoma brain metastases. *Curr Treat Options Neurol.* 2017;19(4):13.

132. Long GV, Trefzer U, Davies MA, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multicentre, open-label, phase 2 trial. *Lancet Oncol.* 2012;13(11):1087–1095.

133. McArthur GA, Maio M, Arance A, et al. Vemurafenib in metastatic melanoma patients with brain metastases: an open-label, single-arm, phase 2, multicentre study. *Ann Oncol.* 2017;28(3):634–641.

134. Long GV, Grob JJ, Nathan P, et al. Factors predictive of response, disease progression, and overall survival after dabrafenib and trametinib combination treatment: a pooled analysis of individual patient data from randomised trials. *Lancet Oncol.* 2016;17(12):1743–1754.

135. Davies MA, Saiag P, Robert C, et al. Dabrafenib plus trametinib in patients with BRAFV600-mutant melanoma brain metastases (COMBI-MB): a multicentre, multicohort, open-label, phase 2 trial. *Lancet Oncol.* 2017;18(7):863–873.

136. Margolin K, Ernstoff MS, Hamid O, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase 2 trial. *Lancet Oncol.* 2012;13(5):459–465.

137. Kluger HM, Chiang V, Mahajan A, et al. Long-term survival of patients with melanoma with active brain metastases treated with pembrolizumab on a phase II trial. *J Clin Oncol.* 2019;37(1):52–60.

138. Tawbi HA, Forsyth PA, Algazi A, et al. Combined nivolumab and ipilimumab in melanoma metastatic to the brain. *N Engl J Med.* 2018;379(8):722–730.

139. Long GV, Atkinson V, Lo S, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicentre randomised phase 2 study. *Lancet Oncol.* 2018;19(5):672–681.

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

141. Gonzalez M, Hong AM, Carlino MS, et al. A phase II, open label, randomized controlled trial of nivolumab plus ipilimumab with stereotactic radiotherapy versus ipilimumab plus nivolumab alone in patients with melanoma brain metastases (ABC-X Trial). *J Clin Oncol.* 2019;37(15_suppl):TPS9600–TPS9600.

142. Iuchi T, Shingyoji M, Sakaida T, et al. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. *Lung Cancer.* 2013;82(2):282–287.