# 5 Role of Precision Medicine in Patients with CNS Metastasis

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## Introduction

Brain metastases (BMs) are the most common central nervous system (CNS) malignancy, and are widely felt to represent a grim prognosis. Progression of intracranial disease is the cause of death in up to 50% of patients with clinically significant BM [1]. The reported incidence of BM is 10–30% in all adults with cancer, and up to 40% of patients with metastatic cancer [1]. However, these estimates likely underestimate the true incidence in the current era of modern cancer therapies. Over the past decade, the incidence of BM has risen due to improved diagnostic testing that facilitates detection of asymptomatic BM and increased patient survival through better tolerated and more effective treatment strategies [1]. Lung cancer (39–56%), breast cancer (13–30%), and melanoma (6–11%) are among the most likely systemic cancers to cross into the CNS [2]. Less common, but still reported, are gastrointestinal cancers (3–8%) and renal cell carcinoma (2–4%) [2].

Prognosis for BM is poor, with a median survival ranging from 3 to 27 months after detection, depending on the primary malignancy [1]. Treatment options are limited and involve a multidisciplinary approach including surgical resection, radiotherapy, and systemic treatment. Historically, patients with BM were treated with whole brain radiotherapy (WBRT); however, recent data in specific clinical scenarios where there are effective systemic treatment options suggest that deferring WBRT may be reasonable due to a lack of overall survival benefit and the associated neurotoxicity. At present, treatment for BM is often case-specific and dependent on many factors, such as performance status of the patient, as well as the number, location of, and primary tumor type of BM [3]. Surgical resection followed by radiotherapy is generally the standard of care for solitary or large (>3 cm) symptomatic lesions [1, 3]. Stereotactic radiosurgery (SRS) alone is frequently used for oligometastatic disease, which is commonly defined as up to four BMs [1, 3]. Hippocampal-sparing WBRT, which may have a lower risk of neurocognitive side effects [1], can be considered in patients with multiple disseminated BMs and leptomeningeal spread of disease.

It is generally recommended that patients with active extracranial disease receive systemic therapy after local brain therapy, as surgery and radiation alone are not curative. Differential responses to these treatments for intracranial and extracranial disease are often observed, where systemic disease is adequately controlled with progression of

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intracranial tumor burden [4]. The reasons behind this differential response are multifactorial and not completely understood. One reason may be inadequate penetration of these systemic therapies [4]. However, even with the use of new agents with known intracranial efficacy, the majority of patients progress in the brain. This issue illustrates an incomplete understanding of BM tumor biology and the drivers that mediate blood-brain barrier (BBB) penetration and CNS proliferation. This is due, in part, to a relative paucity of clinical trials evaluating systemic therapies in BM, due largely to the exclusion of patients with BM from clinical trials due to perceived poor prognosis. Another barrier is the lack of understanding of the genomic drivers behind development of BM and longitudinal changes in tumor genomics and physiology during treatment. Direct tissue analysis to understand these changes can be challenging due to the surgical risk associated with tissue sampling or inoperable location within the brain. Noninvasive methods of genomic profiling of BM are currently under development and detailed in this review.

In the current era of precision medicine, choice of treatment for many systemic cancers has become increasingly personalized and dependent on the molecular or genomic characterization of systemic cancer. To this end, improved control of both intracranial and extracranial tumor burden has been observed with targeted therapy and immunotherapy. In this review, we present current efforts to characterize the genomic drivers and heterogeneity of BM, as compared to the primary tumor, using modern sequencing techniques. A better understanding of these genomic alterations will lead to more precise tailoring of current treatments and new therapeutic approaches. Additionally, we will present current knowledge of targeted therapies for BM of systemic cancers of different histologies.

## Genetic Heterogeneity in Brain Metastases

Selection of targeted therapy for BM has traditionally relied on genomic analysis of the initial primary tumor resection to identify actionable mutations. Recent studies, however, have demonstrated significant genomic heterogeneity between BM and the paired primary tumor [5]. In a study of 86 patients in which BM, primary tumors, and normal tissue were analyzed by whole exome sequencing, 46 (53%) patients had distinct, potentially actionable mutations in the BM not detected in the paired primary tumor [5]. The vast majority of BMs, however, are clonally related to the primary tumor, as only 4/86 (4.6%) specimens were shown to be unrelated to the primary lesion [5]. Similarly, distal extracranial and regional lymph node metastases were also found to be clonally related to the primary tumor, but highly divergent from BM [5]. These findings suggest that branched evolution, or the divergent propagation of multiple subclonal populations arising from a common ancestor [6, 7], likely explains genomic differences between the primary tumor and different metastases as well as the phenomenon of locoregional genomic heterogeneity. During branched evolution, tumors will acquire hundreds, if not thousands, of genetic alterations, a minority of which is driver mutations that confer a selective growth advantage to clones harboring the mutation [7]. These advantageous mutations allow for the development and proliferation of subclonal populations.

The exact genomic signatures required for CNS metastases and proliferation are still unclear. Interestingly, spatially and temporally separated BM from the same patient possess a more homogenous genomic signature when compared to each other as opposed to the primary tumor [5], suggesting that specific genomic alterations may be integral for the brain metastatic process. To this end, several studies have shown that upregulation of specific pathways such as phosphatidylinositol-4,5-bisphosphate 3-kinase (Pi3K) [8], epidermal growth factor receptor (EGFR) [8], or human EGFR 2 (HER2) [9] is associated with cancer cells crossing into the blood-brain barrier (BBB) and proliferating within the CNS. Furthermore, alterations in the cyclin-dependent kinase (CDK) pathways, such as *CDKN2A* loss and *CDK4/6* amplification, have also been implicated in CNS metastases [5]. The exact role that these genomic alterations play in BM pathogenesis is not known

at this time, and remains an active area of research. For example, are these genetic alterations simply related to the underlying histology of the primary tumor, or is dysregulation of these pathways necessary for CNS spread and proliferation? In support of the latter, a recent study demonstrated loss of phosphatase and tensin homolog (PTEN), a tumor suppressor gene, expression in human tumor cells with normal PTEN expression after dissemination to the brain but not to other organs [10]. Furthermore, the PTEN deficient level in BM tumor cells was restored after leaving the brain microenvironment. This finding seems to indicate that certain genomic changes are needed for CNS proliferation, a topic worthy of further prospective study for confirmation.

Divergent evolution of BM has important therapeutic implications. This genomic heterogeneity likely explains the divergent response seen in intracranial and extracranial disease burden in response to targeted therapies. In many cases, actionable mutations for CNS metastases may only be present in BM. As BMs are not always resected for diagnostic purposes due to the morbidity associated with tissue sampling, CNS therapeutic strategies are often made from analysis of the primary tumor or extracranial metastasis. This assumption can result in sampling bias, given frequent BM genomic divergence from extracranial tissue samples. If available, actionable targetable alterations for BM purposes should be assessed from BM tissue analysis. It should be noted that whether specific systemic targeted therapies hold prophylactic or durable therapeutic efficacy for BM is unknown at this time. It is possible that reprogramming of the cancer cell transcriptome by the CNS microenvironment may impact efficacy of systemic therapies in BM. This question requires further study to fully answer.

As BM tissue analysis or serial brain biopsies are not always feasible, continued development of noninvasive techniques that shed light on genomic and physiologic changes as a result of treatment are critical. Several such methods, such as liquid biopsies, circulating tumor cells, or cell-free deoxyribonucleic acid (DNA), are described further below. Such techniques may help us better understand the breadth of genomic heterogeneity in BM and will result in further refinement of current treatment strategies.

## Genomic Profiling of Brain Metastases

The recent introduction of targeted therapies and checkpoint inhibitors has resulted in unprecedented durable responses for many systemic cancers, including those with a high propensity for BMs, such as melanoma, non-small-cell lung cancer, and breast cancer. As such, cancer treatment has become increasingly personalized and dependent on the molecular and genomic traits of each patient's cancer. Similarly, identification of these actionable mutations within BM holds great potential to drastically alter outcomes. Unfortunately, determining the exact genomic signature for BM can be unwieldy as this frequently entails direct tissue analysis. As BM often possesses targetable mutations not present in the primary tumor or distal extracranial metastases [5], genomic analysis of these extracranial sites can miss these genomic alterations and thus targeted therapy opportunities for BM. This clinical conundrum illustrates a critical need for noninvasive and clinically practical methods to capture intracranial molecular profiling. Such a biomarker would provide a better understanding of temporal evolution of BM, inform choice of treatment, and aid in early identification of drug-resistant mutations.

Molecular analysis of circulating tumor DNA (ctDNA) in plasma is currently used for several systemic cancers as a noninvasive tool for genomic profiling and monitoring treatment response [11–13]. However, tumor DNA was found to be either absent or only present in small amounts in the plasma of patients with primary brain tumors or solid tumor BM [12]. In such cases, molecular analysis of ctDNA isolated from cerebrospinal fluid (CSF) is emerging as a promising biomarker. The fraction of cell-free ctDNA in the CSF is higher than in plasma due to the relative absence of background normal DNA in CSF [13]. This allows for the detection of somatic mutations in the CSF with moderate sequence

coverage, whereas plasma ctDNA sequencing requires very deep sequence coverage to achieve similar sensitivities for detecting mutations occurring at low allele frequencies. Additionally, mutations present only in BM and not in the extracranial tumors were represented in CSF ctDNA [12]. Lastly, tumor DNA burden in CSF ctDNA was observed to change during treatment [12]. Mutant allelic frequency of CSF ctDNA decreased with tumor response to treatments and increased with progression. While current methods using CSF ctDNA for detection of all types of mutations still require optimization, the above data suggests that CSF ctDNA may soon develop into a clinical tool for BM genomic analysis.

Additional biomarkers that reflect the BM genomic signature are currently under development. One such example is an exosome, an extracellular vesicle released from the cell upon fusion of an intermediate endocytic compartment with the plasma membrane. These vesicles are felt to be a conduit for intercellular communication and may contain genomic data consistent with a tumor's molecular properties. The burgeoning field of radiogenomics, or the relationship between an imaging-derived phenotype and genomic data, may also be a promising way to noninvasively monitor for genomic alterations. Using these correlations with serial imaging may shed light on alterations in tumor biology as a result of treatment. If optimized, radiogenomics may assist in the early detection of drug-resistant mutations and thus inform a change to a more efficacious treatment regimen. Both fields are largely in their infancy, and currently associated with significant limitations.

## Non-Small-Cell Lung Cancer

Non-small-cell lung cancer (NSCLC) is the leading cause of cancer mortality worldwide, accounting for 18.2% of total deaths from cancer [14]. Furthermore, NSCLC, adenocarcinoma in particular, is the most common primary malignancy to metastasize to the brain [3]. Approximately 25–30% of NSCLC patients will develop BM during the course of their disease [15]. Larger tumor size, lymphovascular space invasion, and hilar lymph node involvement are associated with an increased risk of BMs [16]. Unfortunately, despite an aggressive multimodality treatment approach combining platinum-based chemotherapy, radiation, and surgery, prognosis remains poor. The reported 1-year mortality rate after developing BM ranges from 81% to 90% [14]. In addition, approximately 40–50% of patients with complete initial responses to therapy will develop BM [17]. Over the past decade, NSCLC management has been revolutionized by the identification of oncogenic driver mutations in anaplastic lymphoma kinase (*ALK*) and epidermal growth factor receptor (*EGFR*) and the development of targeted therapies, resulting in unprecedented response rates.

### NSCLC: EGFR Tyrosine Kinase Inhibitor

Activating mutations in *EGFR* are generally found in NSCLC patients with the following characteristics: female gender, age <35 years, Asian descent (in about 40%), history of never or light-smoking and adenomatous histology [18]. In such patients, *EGFR* mutation testing is recommended. *EGFR* mutations render these tumors sensitive to EGFR tyrosine kinase inhibitors (TKIs), which results in significantly improved outcomes when compared to platinum-based combination chemotherapy [19]. For patients without a non-squamous histology *EGFR* mutation testing is not recommended due to extremely low likelihood of positivity, unless they are non-smokers [18].

First- and second-generation EGFR TKIs selectively target the *EGFR* receptor through competitive, reversible binding at the tyrosine kinase domain, and are currently first-line therapy for *EGFR*-mutant NSCLC [19, 20]. Erlotinib and gefitinib are among the most commonly used EGFR first-generation TKIs. However, the majority of patients with initial response to EGFR TKIs had disease progression due to an acquired resistance within 1–2 years [21]. The development of an additional *EGFR* mutation, most com-

monly the threonine-to-methionine substitution at position 790 on exon 20 (T790M), is responsible for approximately 60% of this acquired resistance [22]. Third generation TKIs, such as osimertinib and rociletinib, have shown promising activity for these resistant *EGFR*-mutant types [23].

Presently, data on the efficacy of *EGFR* TKIs in treating NSCLC BMs is hopeful, but limited. Barriers to an accurate evaluation are the lack of clinical trials studying targeted therapies in BM, and regional genomic heterogeneity—as an *EGFR*-mutant status in the primary tumor is not always present in BM. Nonetheless, available data suggests that these agents likely have some CNS activity. Recent preclinical data demonstrates intracranial activity of afatinib, a second-generation *EGFR* TKI and an irreversible ErbB family inhibitor [24]. Post-hoc subgroup analysis from the LUX-Lung 3 and LUX-Lung 6 studies, which allowed patients with asymptomatic BM to be enrolled, showed survival benefit from treatment with afatinib compared to platinum-based chemotherapy. Progression free survival (PFS) (8.2 vs. 5.4 months) and objective response rate (ORR) (70–75% vs. 20–28%) were significantly better with afatinib than platinum-based chemotherapy [25]. Another small phase II prospective trial exploring *EGFR* TKIs in BM reported an 83% ORR with first-generation TKIs [26]; however, other studies have reported more modest responses [27]. For acquired resistance, a recent study demonstrated superior BBB penetration with osimertinib than with gefitinib or afatinib, as well as sustained BM regression in an *EGFR*-mutant mouse model [28].

Taken together, EGFR TKIs, especially osimertinib, appear to have positive CNS activity. How to apply these findings in the context of surgical resection and radiotherapy still remains unclear. It seems reasonable to incorporate EGFR TKIs up front in asymptomatic BMs and to consider delaying surgery or radiation until BM progression to minimize adverse effects. Further prospective trials evaluating EGFR TKIs and sequential approaches with brain radiotherapy to optimize CNS efficacy and minimize radiation-induced neurotoxicity are needed.

## NSCLC: Anaplastic Lymphoma Kinase (ALK) Tyrosine Kinase Inhibitors

The discovery of the *ALK* gene rearrangement and development of genetically driven therapies targeting this aberration have led to tremendous progress in treating NSCLC. The most common rearrangement arises from a fusion between *ALK* and the echinoderm microtubule-like protein 4 (*EML4*) gene. This results in an oncogenic tyrosine kinase with constitutive activity, and is found in up to 5% of NSCLC [29]. BM is a relatively common occurrence in *ALK*-rearranged NSCLC, with incidence quoted at 23.8% at time of diagnosis and 58.4% at 3 years [30]. As with EGFR, *ALK* translocations are associated with younger age, history of light or no smoking, and adenocarcinoma histology [31]. Consequently, testing for *ALK* is highly recommended for such patients [2], as the presence of an *ALK*-mutation is correlated with response to ALK TKIs.

Crizotinib, a first-generation ALK TKI that also has activity against *MET* and *ROS1* [31], is superior to standard-of-care chemotherapy for management of systemic ALK-rearranged NSCLC [32]. While assessing ALK TKIs for CNS efficacy is limited due to exclusion of BMs from many randomized clinical trials, crizotinib likely holds some CNS efficacy. In the PROFILE 1005 and 1007 studies, patients with untreated asymptomatic BMs were included in a pooled retrospective analysis. For these patients, intracranial disease control rate was noted to be 56% at 12 weeks, with a median time to CNS progression of 7 months [31]. In PROFILE 1014, a randomized phase III trial of crizotinib versus platinum-based chemotherapy, patients with stable treated BMs were allowed to enroll with CNS efficacy as a secondary endpoint. In this cohort, CNS disease control rate for patients with BM was significantly higher with crizotinib at 12 weeks (85% vs. 45%) and median PFS was significantly longer (9 vs. 4 months) [33].

Second-generation ALK TKIs are promising options for *ALK*-rearranged NSCLC patients who develop resistance to crizotinib, and are also felt to have improved CNS efficacy. Of these agents, alectinib and ceritinib are among those

with the strongest evidence for BM. Preliminary findings from the J-ALEX study, a Japanese phase III trial that recruited ALK-inhibitor naïve patients with *ALK*-rearranged NSCLC, reported that the alectinib cohort had yet to reach median PFS, while the crizotinib cohort's median PFS was 10.2 months [34]. Two other phase II studies with alectinib demonstrated CNS response rates up to 75% and median CNS disease response durations of 10–11 months [35, 36]. In the ASCEND-1 study, 94 patients with *ALK*-rearranged NSCLC BM were retrospectively analyzed. Of this cohort, 79% of ALK TKI-naïve and 65% of ALK TKI-pretreated patients had intracranial response to ceritinib [37]. Newer ALK TKIs such as lorlatinib and brigatinib likely have even better brain efficacy. As with first-generation ALK TKIs, further work is needed to determine utility of these treatments in combination with radiotherapy with the intent of maximizing CNS efficacy.

### NSCLC: Immunotherapy

Immune checkpoint inhibitors have emerged as an option for patients with advanced NSCLC without an actionable driver mutation (i.e., EGFR and ALK), or for those with actionable mutations that have progressed on next-generation targeted agents [38]. Immune checkpoints, which refer to inhibitory pathways that modulate the physiologic immune response to minimize collateral damage and thus maintain self-tolerance, are co-opted by tumors. For example, the interaction of programmed death 1 (PD-1) receptor on activated T cells with programmed death ligand 1 (PD-L1) on tumor cells leads to T-cell inactivation, which prevents the immune system from attacking the tumor cell [38]. Nivolumab and pembrolizumab are anti-PD1 monoclonal antibodies that have been shown to improve survival outcomes in patients with metastatic NSCLC without actionable mutations, as compared to docetaxel-based chemotherapy [39, 40]. Furthermore, pembrolizumab demonstrated PFS and overall survival (OS) superiority to platinum-based chemotherapy as first-line therapy in patients with NSCLC with greater than 50% PD-L1 expression, suggesting that PD-L1 expression may be a predictive biomarker for response [41].

Many immunotherapy trials for NSCLC, to date, have excluded patients with active brain metastases. However, a recent early analysis of a phase II trial investigating activity and safety of pembrolizumab in NSCLC and melanoma patients with untreated or progressive BMs showed encouraging results. Patients with NSCLC had tumor tissue positive for PD-L1 expression. In this study, 33% (6 of 18) of NSCLC patients had durable intracranial response without high-grade adverse events [42]. Further randomized prospective studies are needed to investigate these promising options for brain metastases.

## Breast Cancer

Breast cancer is the most common cancer in women and the second-leading cause of cancer-related death in women [3]. It is also the second most common cancer to metastasize to the brain, after NSCLC [1]. The exact incidence of BM from breast cancer in the current era of modern therapies is not clearly defined; however, it is estimated that between 10% and 45% of breast cancer patients will be affected by BM during their disease course, depending on breast tumor subtype [43]. This number will likely increase as overall survival improves with newer, more durable, therapies.

As expected, prognosis for BM in breast cancer remains poor. A large retrospective study identified older age, Karnofsky Performance Status (KPS), and tumor subtype as prognostic factors [44]. Within breast cancer, there are four main tumor subtypes. Basal subtype [estrogen receptor (ER), progesterone receptor (PR), and HER2 negative; also referred to as "triple negative"] has the worst prognosis, with a median OS of 5 months after developing BM [44]. Luminal A (ER- and/or PR-positive, HER2-negative, low levels of Ki-67) are generally low-grade tumors with the best prognosis [44]. Other subtypes include luminal B (ER- and/or PR-positive, and

either HER2-positive or HER2-negative with high levels of Ki-67) and HER2-enriched (ER/PR-negative and HER2-positive). Patients with triple-negative and HER2-enriched breast cancer are at highest risk of CNS metastases [44]. Current management of BM from breast cancer is similar to those of other primary cancers, and includes consideration of systemic therapies in addition to surgical resection and radiation.

In this section, we describe current targeted therapies for breast cancer. Triple negative breast cancer (TNBC) is especially challenging to treat due to lack of clinically actionable genomic alterations and nondurable response to systemic chemotherapy [45]. For this cohort, there has been a growing pool of novel targets as gene sequencing has become more readily accessible. One promising target for TNBC is poly ADP-ribose polymerase (PARP), a family of proteins involved in DNA repair and genomic stability. Histologic studies have shown similarities between the pathological and clinical features of TNBC- and BRCA-associated cancers [45]. Interestingly, BRCA-1 and BRCA-2 mutant cell lines have been shown to be exquisitely sensitive to PARP inhibition [46]. Several PARP inhibitors (i.e., olaparib and veliparib) are currently being evaluated in the adjuvant, neoadjuvant, and metastatic setting for the subset of TNBC with BRCA-1 or BRCA-2 mutations.

## Breast Cancer: HER2 Antibodies and TKIs

HER2 is a member of the human epidermal growth factor receptor family, which consists of four membrane-bound receptor tyrosine kinase implicated in multiple signaling cascades that mediate cell proliferation and apoptosis. This protein is overexpressed in 20% of all breast cancer patients [47]. HER2-directed therapies, such as trastuzumab, lapatinib, pertuzumab, and T-DM1 (ado-trastuzumab emtansine, an antibody-drug conjugate consisting of trastuzumab linked to the cytotoxic agent DM1), significantly improve PFS and OS of patients with HER2-positive metastatic breast cancer. Furthermore, HER2-overexpression is associated with an increased risk of BM, as approximately 30–50% of patients with HER2-positive breast cancer will develop BM during their disease course [48]. The propensity of HER2-positive breast cancer for CNS relapse may be related to improved survival of patients with HER2-directed therapy, the limited CNS penetration of HER2-directed agents, and perhaps the neurotropism of HER2-positive breast cancer [48]. As with other types of primary tumors, temporal and spatial genomic heterogeneity are seen with breast cancer BM. A retrospective study showed that 24% of 182 patients with HER2-positive primary breast cancer had HER2-negative metastatic disease [49]. There is also evidence to suggest that BM commonly occurs in patients with HER2-positive breast cancer that is otherwise systemically well controlled with HER2-directed therapy [48]. As with other types of systemic cancers, these findings illustrate the necessity of repeat genomic analysis on BM tissue if clinically feasible.

Like most other monoclonal antibodies, trastuzumab, which targets the HER2 receptor, has limited CNS activity due to its inability to cross the intact BBB [48]. Consequently, adjuvant radiation with trastuzumab, pertuzumab, and T-DM1 are all being investigated as options for HER2-positive BM. A recent pharmacokinetic study demonstrated improved CNS penetration of trastuzumab after BBB disruption by radiation. The ratio of the CSF to plasma levels of trastuzumab improved significantly from 1:420 before radiotherapy to 1:76 after radiotherapy [50]. Pertuzumab, another monoclonal antibody against the HER2 receptor, likely has some synergistic CNS antitumor efficacy in combination with trastuzumab and docetaxel, as shown in the CLEOPATRA trial, a randomized phase III placebo-controlled trial of pertuzumab in metastatic HER2-positive breast cancer. The median time to development of BMs as first site of disease progression was significantly longer in the pertuzumab arm compared to the placebo arm (15.0 vs. 11.9 months), and the median OS was 56.5 months in the pertuzumab arm, compared to 40.8 months in the placebo arm [51]. Other small case series have also demonstrated

some efficacy for pertuzumab-containing regimens in BM from HER2-positive breast cancer BM [52, 53]. Finally, several retrospective studies indicate some potential activity for the antibody-cytotoxin conjugate T-DM1 in CNS disease [54], but clear prospective evidence is lacking.

Lapatinib is a dual small-molecule HER2 and EGFR TKI that has shown some ability to cross a disrupted BBB. A novel PET imaging study using radiolabeled lapatinib demonstrated increased levels of lapatinib in brain metastases as compared to normal brain tissue [55]. Lapatinib has demonstrated partial response of CNS disease to a modest degree as adjuvant monotherapy (CNS ORR 6% [56]) and in combination with capecitabine (CNS ORR 20–38% in pretreated patients [57, 58]). This CNS antitumor efficacy is augmented in treatment-naïve patients with HER2-positive breast cancer (CNS ORR 65% [59]). Neratinib, an irreversible HER1, HER2, and HER4 TKI, also may have CNS efficacy in HER2-positive metastatic disease. The NEfERTT trial, a randomized phase III trial of patients with metastatic HER2-positive breast cancer, noted significantly lower rates of CNS progression and delayed time to CNS metastases with the neratinib-paclitaxel combination than with trastuzumab-paclitaxel, although the two groups had similar OS [60]. Further studies evaluating these regimens are ongoing.

## Breast Cancer: Additional Mutations

Sequencing studies of BM from breast cancer demonstrated that actionable mutations in the phosphoinositide 3-kinase/protein kinase B/rapamycin (Pi3K/AKT/mTOR) pathways are common [5]. This pathway regulates several cellular functions in cancer, most notably cell growth and proliferation. Increased activation of this pathway is one hypothesized mechanism of resistance to hormonal therapy. Everolimus, an mTOR inhibitor, is currently being studied for breast cancer BM. The breast cancer trials of OraL EveROlimus-3 (BOLERO-3) trial showed that triple therapy with everolimus, trastuzumab, and vinorelbine was superior to placebo, trastuzumab, and vinorelbine in trastuzumab-resistant advanced HER2+ breast cancer [61]. Another large phase III trial showed that everolimus combined with an aromatase inhibitor improved PFS in heavily pretreated hormone receptor-positive advanced breast cancer [62]. While these trials excluded brain metastases, these results may perhaps be generalized to BM as everolimus has been demonstrated to possess CNS penetration in patients with primary brain tumors [63]. Clinical trials evaluating the role of everolimus and other therapies targeting the Pi3K and mTOR signaling pathways in management of breast cancer BM are ongoing.

Alterations in the CDK pathway are common in breast cancer brain metastases [5]. Activation of CDK4 and CDK6 by cyclin D results in cell proliferation by facilitating G1 phase progression and transition from G1 to S phase in the cell cycle [48]. CDK inhibitors, such as ribociclib, palbociclib, and abemaciclib, have demonstrated success in hormone-receptor positive breast cancer [64]. Recent preclinical studies have shown good CNS penetration of abemaciclib, and some efficacy for breast cancer BM as demonstrated by several case series [65]. Current trials are further investigating the efficacy of these agents.

## Melanoma

Melanoma is the third most common systemic cancer to metastasize to the brain [3]. Approximately 50% of patients with stage IV melanoma will develop BM during the course of their disease [1, 3]. As with other systemic malignancies, prognosis of BM in metastatic melanoma is poor due to significant neurologic morbidity. Median OS after the diagnosis of BM has historically been about 4.7 months, although a recent retrospective analysis reported improvement of median OS to 7.7 months with the recent use of targeted therapies [66].

## Melanoma: Mitogen-Activated Protein Kinase (MAPK) Pathway

Approximately 50% of patients with metastatic melanoma will have an activating mutation in *BRAF*, a serine/threonine protein kinase within the MAPK signaling pathway [67]. BRAF is a key regulator of cell growth, division, and differentiation, and when inactive can result in downstream constitutive activation of the MAPK pathway. This provides a basis for the mutational activation and uncontrolled tumor growth for multiple cancers, and thus a potential target for selective inhibition.

In melanoma, the most common *BRAF* mutation is the substitution of valine for glutamic acid (V600E), comprising nearly 90% of all BRAF mutations in melanoma [67]. The second most common *BRAF* alteration is the valine for lysine substitution (V600K), which represents 5–6% of cases. *BRAF*-mutant melanomas are generally more aggressive and may confer a higher risk of developing BM [67]. There are currently two FDA-approved BRAF inhibitors for systemic melanoma: vemurafenib and dabrafenib [67]. BRAF inhibitors have markedly improved OS for patients with *BRAF*-mutant metastatic melanoma. This response, however, is not usually durable [66]. As with other systemic tumors, current BM genomic sequencing studies indicate that the development of treatment-resistant genomic alterations contributes to treatment failure.

Evidence for dabrafenib and vemurafenib in BM efficacy is limited, as many large phase III trials excluded CNS disease. Nonetheless, these agents likely hold some CNS efficacy. The BREAK-MB trial, a multicenter phase II trial with 172 patients with *BRAF*-mutant melanoma with at least one asymptomatic brain metastasis, showed that dabrafenib had activity for patients with either untreated or pretreated BM. For both groups, there was a response rate of >30% with improvement in OS and PFS [68]. In a retrospective study of 27 patients, vemurafenib resulted in an intracranial response rate of 71%. The median intracranial PFS was 4.6 months and median OS was 7.5 months [69]. Interestingly, genomic sequencing analysis of BRAF-inhibitor resistant BM revealed genomic alterations resulting in activation of the Pi3K/AKT pathway [70].

Mitogen-activated protein (MEK) kinase is downstream of *BRAF* in the MAPK pathway, and is frequently activated by members of the Pi3K pathway as a resistance mechanism from BRAF inhibition. To prevent resistance, BRAF inhibitors are frequently combined with MEK inhibitors, such as trametinib and cobimetinib, in metastatic melanoma. When BRAF inhibitors were combined with MEK inhibitors, treatment efficacy was further potentiated in patients with *BRAF* mutant extracranial metastatic melanoma, as evidenced by improved PFS (2 years) and OS (3 years) [71–73]. Dual BRAF and MEK inhibitions for brain metastases are currently being evaluated in clinical trials.

## Melanoma: Pi3K/AKT/mTOR Pathway

Genomic analysis of 16 pairs of patient-matched melanoma brain metastases and extracranial metastases demonstrated increased activation of the Pi3K/AKT/mTOR pathway specific to BM [8]. Preclinical and animal studies using a Pi3K inhibitor, BKM120, demonstrate growth inhibition rates of up to 80% and induced apoptosis in vitro and inhibition of tumor growth of human brain metastatic melanoma cells within brains of nude mice [74]. These findings suggest that an alteration in the Pi3K pathway, for reasons unknown at present, may make a tumor more at risk for CNS spread and proliferation. Furthermore, Pi3K inhibitors may be a potential therapeutic option worthy of prospective clinical trials for metastatic melanoma.

## Melanoma: Immunotherapy

Unprecedented treatment advances for patients with advanced-stage melanoma have occurred recently with the advent of immunotherapy. High-dose interleukin-2 had early success [75],

but was frequently associated with severe toxicities and was consequently limited only to patients with excellent performance status. Ipilimumab, an anti-cytotoxic T-lymphocyte-associated protein 4 (CTLA-4) antibody, received FDA approval in 2011 after a landmark study in 2010 demonstrated improved patient outcomes in unresectable stage III or IV melanoma [76]. Systemic response rates for ipilimumab have ranged from 10% to 15%, with improved response in those with BRAF-wild type melanoma [77, 78]. About 20% of patients with response to ipilimumab were long-term survivors, measured on the order of years [79, 80]. Soon afterward, two anti-PD-1 antibodies, nivolumab and pembrolizumab, were approved by the FDA for metastatic melanoma. Subsequent clinical testing with PD-1 checkpoint blockade demonstrated improved outcomes with less toxicity as compared to ipilimumab [81]. Nivolumab, with a PFS of 6.9 months, was more effective than ipilimumab monotherapy, which displayed a median PFS of 2.9 months [81]. Additionally, pembrolizumab or nivolumab monotherapy were associated with ORR ranging from 33% to 57%, with the majority of responses being durable [77, 82]. In a recent phase III trial of patients with advanced melanoma without BM, the combination of nivolumab and ipilimumab achieved a median PFS of 11.5 months, superior to either monotherapy, but was also associated with more high-grade toxicity (59% for combination ipilimumab/nivolumab vs. 21% with nivolumab) [77].

More data are emerging that checkpoint inhibitors likely possess some efficacy within the CNS. In a phase II study of ipilimumab in 72 melanoma patients with BM, the disease control rate was 24% in patients who were neurologically asymptomatic and not on corticosteroids. One- and two-year survival rates were 31% and 26% in this cohort [80]. Furthermore, there is increasing data that suggests improved OS when SRS is used with checkpoint inhibitors. One retrospective analysis found that the 2-year survival rate of those receiving SRS plus ipilimumab was 47.2%, compared with 19.7% in those who received SRS alone [83]. Another retrospective study of 26 patients with melanoma BM noted an 85% local BM control and a median OS of 11.8 months with nivolumab and SRS to BM [84]. Two recent phase II studies, specifically tailored for patients with melanoma BM, provide even stronger evidence of checkpoint inhibitor efficacy. One study tested ipilimumab and nivolumab in 74 patients with at least one measurable, nonirradiated, asymptomatic BM. Here, the rate of intracranial clinical benefit (57%) was concordant to that of extracranial benefit (56%) with a 20% complete response rate and 30% partial response rate intracranially [85]. Another study with a similar cohort found that combination ipilimumab and nivolumab had an intracranial response rate of 46% (16 of 35) and single-agent nivolumab resulted in an intracranial response rate of 20% (5 of 25) [86]. Similar to prior trials, the combination of ipilimumab and nivolumab was associated with more high-grade adverse events (54% vs. 16% for nivolumab monotherapy) [86].

Despite these promising results, predictive biomarkers of response are desperately needed for more precise tailoring of existing therapies, especially given the high risk of adverse events. Genomic sequencing of melanoma BMs are being analyzed with the hope of identifying mutational profiles associated with better prognoses.

## Conclusion

Brain metastases represent an understudied and underserved area within oncology. This entity is associated with poor prognosis, due to significant neurologic morbidity and current lack of durable CNS-directed therapies. Consequently, better treatments for brain metastases are critically necessary, as incidence is rising as therapies for systemic cancer improve. One major reason for current treatment difficulties is the paucity of clinical trials evaluating systemic treatments for brain metastases, due largely to exclusion of patients with CNS disease. Recently, next-generation targeted agents and immunotherapies have demonstrated improved tolerability and promising response rates for CNS disease.

Current trials evaluating these therapeutic strategies specifically for brain metastases are underway and desperately needed to optimize treatment.

Another breakthrough for brain metastases has been the recognition of spatial and temporal genomic heterogeneity across different metastatic sites. Recent genomic analyses have demonstrated the presence of actionable driver mutations within brain metastases not present in the paired primary tumor. This genomic heterogeneity likely contributes to the clinically observed divergent response seen between intracranial and extracranial disease burden. As brain metastasis tissue analysis is not always feasible, noninvasive methods to obtain genomic information are necessary to guide personalized genomic-directed therapy for brain metastases. Novel approaches such as cell-free circulating tumor DNA in the CSF and radiogenomics are under development and promising. These methods, if optimized for clinical use, may be repeated during a treatment course to help determine response and to assist in the early detection of drug-resistant mutations. Such biomarkers would be a critical step forward in better understanding the temporal evolution of brain metastases and informing choice of treatment.

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## References

1. Brastianos PK, Curry WT, Oh KS. Clinical discussion and review of the management of brain metastases. J Natl Compr Canc Netw. 2013;11:1153–64.
2. Berghoff AS, Bartsch R, Wohrer A, Streubel B, Birner P, Kros JM, et al. Predictive molecular markers in metastases to the central nervous system: recent advances and future avenues. Acta Neuropathol. 2014;128(6):879–91.
3. Nayak L, Lee EQ, Wen PY. Epidemiology of brain metastases. Curr Oncol Rep. 2012;14(1):48–54.
4. Lockman PR, Mittapalli RK, Taskar KS, Rudraraju V, Gril B, Bohn KA, et al. Heterogenous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. Clin Cancer Res. 2010;16(23):5664–78.
5. Brastianos PK, Carter SL, Santagata S, Cahill DP, Taylor-Wener A, Jones RT, et al. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. Cancer Discov. 2015;5(11):1164–77.
6. Navin N, Kendall J, Troge J, Andrews P, Rodgers L, McIndoo J, et al. Tumor evolution inferred by single-cell sequencing. Nature. 2011;472:90–4.
7. Gerlinger M, Rowan AJ, Horswell S, Larkin J, Endesfelder D, Gronroos E, et al. Intratumor heterogeneity and branched evolution revealed by multiregion sequencing. N Engl J Med. 2012;366:883–92.
8. Chen G, Chakravarti N, Aardalen K, Lazar AJ, Tetzlaff MT, Wubbenhorst B, et al. Molecular profiling of patient-matched brain and extracranial melanoma metastases implicates the PI3K pathway as a therapeutic target. Clin Cancer Res. 2014;20(21):5537–46.
9. Bos PD, Zhang XH, Nadal C, Shu W, Gomis RR, Nguyen DX, et al. Genes that mediate breast cancer metastasis to the brain. Nature. 2009;459(7249):1005–9.
10. Zhang L, Zhang S, Yao J, Lowery FJ, Zhang Q, Huang W, et al. Microenvironment-induced PTEN loss by exosomal microRNA primes brain metastasis outgrowth. Nature. 2015;527:100–4.
11. Dawson SJ, Tsui DW, Murtaza M, Biggs H, Rueda OM, Chin SF, et al. Analysis of circulating tumor DNA to monitor metastatic breast cancer. N Engl J Med. 2013;368(13):1199–209.
12. De Mattos-Arruda L, Mayor R, Ng CK, Weigelt B, Martinez-Ricarte F, Torrejon D, et al. Cerebrospinal fluid-derived circulating tumor DNA better represents the genomic alterations of brain tumors than plasma. Nat Commun. 2015;6:8839.
13. Murtaza M, Dawson SJ, Tsui DW, Gale D, Forshew T, Piskorz AM, et al. Non-invasive analysis of acquired resistance to cancer therapy by sequencing of plasma DNA. Nature. 2013;497(7447):108–12.
14. Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin. 2011;61(2):69–90.
15. Mamon HJ, Yeap BY, Janne PA, Reblando J, Shrager S, Jaklitsch MT. High risk of brain metastases in surgically staged IIIA non-small-cell lung cancer patients treated with surgery, chemotherapy, and radiation. J Clin Oncol. 2005;23(7):1530–7.
16. Hubbs JL, Boyd JA, Hollis D, Chino JP, Saynak M, Kelsey CR. Factors associated with the development of brain metastases: analysis of 975 patients with early stage nonsmall cell lung cancer. Cancer. 2010;116(21):5038–46.
17. Chen AM, Jahan TM, Jablons DM, Garcia J, Larson DA. Risk of cerebral metastases and neurological death after pathological complete response to neoadjuvant therapy for locally advanced nonsmall-cell lung cancer: clinical implications for the subsequent management of the brain. Cancer. 2007;109(8):1668–75.

18. Sholl LM, Yeap BY, Iafrate AJ, Holmes-Tisch AJ, Chou YP, Wu MT, et al. Lung adenocarcinoma with EGFR amplification has distinct clinicopathologic and molecular features in never-smokers. Cancer Res. 2009;69(21):8341–8.
19. Mok TS, Wu Y-L, Thongprasert S, Yang C-H, Chu D-T, Saijo N, et al. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. N Engl J Med. 2009;361:947–57.
20. Sequist LV, Yang JC, Yamamoto N, O'Byrne K, Hirsh V, Mok T, et al. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. J Clin Oncol. 2013;31(27):3327–34.
21. Sequist LV, Waltman BA, Dias-Santagata D, Digumarthy S, Turke AB, Fidias P, et al. Genotypic and histological evolution of lung cancers acquiring resistance to EGFR inhibitors. Sci Transl Med. 2011;3(75):75ra26.
22. Yu HA, Arcila ME, Rekhtman N, Sima CS, Zakowski MF, Pao W, et al. Analysis of tumor specimens at the time of acquired resistance to EGFR-TKI therapy in 155 patients with EGFR-mutant lung cancers. Clin Cancer Res. 2013;19(8):2240–7.
23. Janne PA, Yang JC, Kim DW, Planchard D, Ohe Y, Ramalingam SS, et al. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. N Engl J Med. 2015;372(18):1689–99.
24. Hoffknecht P, Tufman A, Wehler T, Pelzer T, Wiewrodt R, Schutz M, et al. Efficacy of the irreversible ErbB family blocker afatinib in epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI)-pretreated non-small-cell lung cancer patients with brain metastases or leptomeningeal disease. J Thorac Oncol. 2015;10(1):156–63.
25. Schuler M, Wu YL, Hirsh V, O'Byrne K, Yamamoto N, Mok T, 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):380–90.
26. Park SJ, Kim HT, Lee DH, Kim KP, Kim SW, Suh C, et al. Efficacy of epidermal growth factor receptor tyrosine kinase inhibitors for brain metastasis in non-small cell lung cancer patients harboring either exon 19 or 21 mutation. Lung Cancer. 2012;77(3):556–60.
27. Porta R, Sanchez-Torres JM, Paz-Ares L, Massuti B, Reguart N, Mayo C, et al. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. Eur Respir J. 2011;37(3):624–31.
28. Ballard P, Yates JW, Yang Z, Kim DW, Yang JC, Cantarini M, et al. Preclinical comparison of osimertinib with other EGFR-TKIs in EGFR-mutant NSCLC brain metastases models, and early evidence of clinical brain metastases activity. Clin Cancer Res. 2016;22(20):5130–40.
29. Guerin A, Sasane M, Zhang J, Culver KW, Dea K, Nitulescu R, et al. Brain metastases in patients with ALK+ non-small cell lung cancer: clinical symptoms, treatment patterns, and economic burden. J Med Econ. 2015;18(4):312–22.
30. Rangachari D, Yamaguchi N, VanderLaan PA, Folch E, Mahadevan A, Floyd SR, et al. Brain metastases in patients with EGFR-mutated or ALK-rearranged non-small cell lung cancers. Lung Cancer. 2015;88(1):108–11.
31. Kwak EL, Bang YJ, Camidge DR, Shaw AT, Solomon B, Maki RG, et al. Anaplastic lymphoma kinase inhibition in non-small-cell lung cancer. N Engl J Med. 2010;363(18):1693–703.
32. Shaw AT, Kim DW, Nakagawa K, Seto T, Crino L, Ahn MK, et al. Crizotinib versus chemotherapy in advanced ALK-positive lung cancer. N Engl J Med. 2013;368(25):2385–94.
33. Costa DB, Shaw AT, Ou SH, Solomon BJ, Riely GJ, Ahn MJ, et al. Clinical experience with crizotinib in patients with advanced ALK-rearranged non-small-cell lung cancer and brain metastases. J Clin Oncol. 2015;33(17):1881–8.
34. Hida T, Nokihara H, Kondo M, Kim YH, Azuma K, Seto T, 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.
35. Shaw AT, Gandhi L, Gadgeel S, Riely GJ, Cetnar J, West H, et al. Alectinib in ALK-positive, crizotinib-resistant, non-small-cell lung cancer: a single group, multicenter, phase 2 trial. Lancet Oncol. 2016;17(2):234–42.
36. Ou SH, Ahn JS, De Petris L, Govindan R, Yang JC, Hughes B, et al. Alectinib in crizotinib-refractory ALK-rearranged non-small-cell lung cancer: a phase II global study. J Clin Oncol. 2016;34(7):661–8.
37. Kim D-W, Mehra R, Tan D, Felip E, Chow L, Camidge P, et al. Activity and safety of ceritinib in patients with ALK-rearranged non-small-cell lung cancer (ASCEND-1): updated results from the multicentre, open-label, phase 1 trial. Lancet Oncol. 2016;17(4):452–63.
38. Raju S, Joseph R, Sehgal S. Review of checkpoint immunotherapy for the management of non-small cell lung cancer. Immunotargets Ther. 2018;7:63–75.
39. Borghaei H, Paz-Ares L, Horn L, Spigel DR, Steins M, Ready NE, et al. Nivolumab versus docetaxel in advanced nonsqaumous non-small-cell lung cancer. N Engl J Med. 2015;373(17):1627–39.
40. Herbst RS, Baas P, Kim DW, Felip E, Perez-Gracia JL, Han JY, et al. Pembrolizumab versus docetaxel for previously treated, PD-L1-positive advanced non-small-cell lung cancer (KEYNOTE-010): a randomized controlled trial. Lancet. 2016;387(10027):1540–50.
41. Reck M, Rodriguez-Abreu D, Robinson AG, Hui R, Csoszi T, Fulop A, et al. Pembrolizumab versus chemotherapy for PD-L1-positive non-small-cell lung cancer. N Engl J Med. 2016;375(19):1823–33.
42. Goldberg SB, Gettinger SN, Mahajan A, Chiang AC, Herbst RS, Sznol M, 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):976–83.

43. 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):2865–72.
44. Sperduto PW, Chao ST, Sneed PK, Luo X, Suh J, Roberge D, 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):655–61.
45. Cleator S, Heller W, Coombes RC. Triple-negative breast cancer: therapeutic options. Lancet Oncol. 2007;8(3):235–44.
46. Farmer H, McCabe N, Lord CJ, Tutt AN, Johnson DA, Richardson TB, et al. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature. 2005;434(7035):917–21.
47. Lin NU, Winer EP. Brain metastases: the HER2 paradigm. Clin Cancer Res. 2007;13(6):1648–55.
48. Venur VA, Leone JP. Targeted therapies for brain metastases from breast cancer. Int J Mol Sci. 2016;17(9):E1543.
49. Niikura N, Liu J, Hayashi N, Mittendorf EA, Gong Y, Palla SL, et al. Loss of human epidermal growth factor receptor 2 (HER2) expression in metastatic sites of HER2-overexpressing primary breast tumors. J Clin Oncol. 2012;30(6):593–9.
50. Stemmler HJ, Schmitt M, Willems A, Bernhard H, Harbeck N, Heinemann V. Ratio of trastuzumab levels in serum and cerebrospinal fluid is altered in HER2-positive breast cancer patients with brain metastases and impairment of blood-brain barrier. Anticancer Drugs. 2007;18(1):23–8.
51. Swain SM, Baselga J, Kim SB, Ro J, Semiglazov V, Campone M, et al. Pertuzumab, trastuzumab, and docetaxel in HER2-positive metastatic breast cancer. N Engl J Med. 2015;372(8):724–34.
52. Senda N, Yamaguchi A, Nishimura H, Shiozaki T, Tsuyuki S. Pertuzumab, trastuzumab, and docetaxel reduced the recurrence of brain metastasis from breast cancer: a case report. Breast Cancer Tokyo Jpn. 2016;23(2):323–8.
53. Koumarianou A, Kontopoulou C, Kouloulias V, Tsionou C. Durable clinical benefit of pertuzumab in a young patient with BRCA2 mutation and HER2-overexpression breast cancer involving the brain. Case Rep Oncol Med. 2016;2016:5718104.
54. Bartsch R, Berghoff AS, Vogl U, Rudas M, Bergen E, Dubsky P, et al. Activity of T-DM1 in HER2-positive breast cancer brain metastases. Clin Exp Metastasis. 2015;32(7):729–37.
55. Saleem A, Searle GE, Kenny LM, Huiban M, Kozlowski K, Waldman AD, et al. Lapatinib access into normal brain and brain metastases in patients with Her-2 overexpressing breast cancer. EJNMMI Res. 2015;5:30.
56. Lin NU, Dieras V, Paul D, Lossignol D, Christodoulou C, Stemmler HJ, et al. Multicenter phase II study of lapatinib in patients with brain metastases from HER2-positive breast cancer. Clin Cancer Res. 2009;15(4):1452–9.
57. Sutherland S, Ashley S, Miles D, Chan S, Wardley A, Davidson N, et al. Treatment of HER2-positive metastatic breast cancer with lapatinib and capecitabine in the lapatinib expanded access programme, including efficacy in brain metastases – the UK experience. Br J Cancer. 2010;102(6):995–1002.
58. Lin NU, Eierman W, Greil R, Campone M, Kaufman B, Steplewski K, et al. Randomized phase II study of lapatinib plus capecitabine or lapatinib plus topotecan for patients with HER2-positive breast cancer brain metastases. J Neurooncol. 2011;105(3):613–20.
59. Bachelot T, Romieu G, Campone M, Dieras V, Cropet C, Dalenc F, et al. Lapatinib plus capecitabine in patients with previously untreated brain metastases from HER-2 positive metastatic breast cancer (LANDSCAPE): a single-group phase II study. Lancet Oncol. 2013;14(1):64–71.
60. Awada A, Colomer R, Inoue K, Bondarenko I, Badwe RA, Demetriou G, et al. Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: the NEfERT-T randomized clinical trial. JAMA Oncol. 2016;2(12):1557–64.
61. Andre F, O'Regan R, Ozguroglu M, Toi M, Xu B, Jerusalem G, et al. Everolimus for women with trastuzumab-resistant, HER2-positive, advanced breast cancer (BOLERO-3): a randomized, double-blind, placebo-controlled phase 3 trial. Lancet Oncol. 2014;15(6):580–91.
62. Baselga J, Campone M, Piccart M, Burris HA III, Rugo HS, Sahmoud T, et al. Everolimus in postmenopausal hormone-receptor-positive advanced breast cancer. N Engl J Med. 2012;366(6):520–9.
63. Franz DN, Belousouva E, Sparagana S, Bebin EM, Frost M, Kuperman R, et al. Efficacy and safety of everolimus for subependymal giant cell astrocytomas associated with tuberous sclerosis complex (EXIST-1): a multi-centre, randomized, placebo-controlled phase 3 trial. Lancet. 2013;381(9861):125–32.
64. Turner NC, Ro J, Andre F, Loi S, Verma S, Iwata H, et al. Palbociclib in hormone-receptor-positive advanced breast cancer. N Engl J Med. 2015;373(3):209–19.
65. Sahebjam S, Rhun EL, Kulanthiavel P, Turner PK, Klise S, Wang HT, et al. Assessment of concentrations of abemaciclib and its major active metabolites in plasma, CSF, and brain tumor tissue in patients with brain metastases secondary to hormone receptor positive (HR+) breast cancer. J Clin Oncol. 2016;34(15_suppl):526.
66. Dagogo-Jack I, Gill CM, Cahill DP, Santagata S, Brastianos PK. Treatment of brain metastases in the modern genomic era. Pharmacol Ther. 2017;170:64–72.
67. Long GV, Menzies AM, Nagrial AM, Haydu LE, Hamilton AL, Mann GJ, et al. Prognostic and clinicopathologic associations of oncogenic BRAF in metastatic melanoma. J Clin Oncol. 2011;29(10):1239–46.

68. Long GV, Trefzer U, Davies MA, Kefford RF, Ascierto PA, Chapman PB, et al. Dabrafenib in patients with Val600Glu or Val600Lys BRAF-mutant melanoma metastatic to the brain (BREAK-MB): a multi-center, open-label, phase 2 trial. Lancet Oncol. 2012;13(11):1087–95.
69. Harding JJ, Catalanotti F, Munhoz RR, Cheng DT, Yaqubie A, Kelly N, et al. A retrospective evaluation of vemurafenib as treatment for BRAF-mutant melanoma brain metastases. Oncologist. 2015;20(7):789–97.
70. Davies MA, Stemke-Hale K, Lin E, Tellez C, Deng W, Gopal YN, et al. Integrated molecular and clinical analysis of AKT activation in metastatic melanoma. Clin Cancer Res. 2009;15(24):7358–46.
71. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Combined BRAF and MEK inhibition versus BRAF inhibition alone in melanoma. N Engl J Med. 2014;371(20):1877–88.
72. Long GV, Stroyakovskiy D, Gogas H, Levchenko E, de Braud F, Larkin J, et al. Dabrafenib and trametinib versus dabrafenib and placebo for Val600 BRAF-mutant melanoma: a multicenter, double-blind, phase 3 randomised controlled trial. Lancet. 2015;386(9992):444–51.
73. Robert C, Karaszewska B, Schachter J, Rutkowski P, Mackiewicz A, Stroiakovski D, et al. Improved overall survival in melanoma with combined dabrafenib and trametinib. N Engl J Med. 2015;371(1):30–9.
74. Meier FE, Niessner H, Schmitz J, Schmid A, Calaminus C, Pichler B, et al. The PI3K inhibitor BKM120 has potent antitumor activity in melanoma brain metastases in vitro and in vivo. J Clin Oncol. 2013;31(15_suppl):e20050.
75. Krieg C, Letourneau S, Pantaleo G, Boyman O. Improved IL-2 immunotherapy by selective stimulation of IL-2 receptor on lymphocytes and endothelial cells. Proc Natl Acad Sci U S A. 2010;107(26):11906–11.
76. Hodi FS, O'Day SJ, McDermott DF, Weber RW, Sosman JA, Haanen JB, et al. Improved survival with ipilimumab in patients with metastatic melanoma. N Engl J Med. 2010;363(8):711–23.
77. Larkin J, Chiarion-Sileni V, Gonzalez R, Grob JJ, Cowey CL, Lao CD, et al. Combined nivolumab and ipilimumab or monotherapy in untreated melanoma. N Engl J Med. 2015;373(1):23–34.
78. Postow MA, Chesney J, Pavlick AC, Robert C, Grossmann K, McDermott D, et al. Nivolumab and ipilimumab versus ipilimumab in untreated melanoma. N Engl J Med. 2015;372(21):2006–17.
79. Tazi K, Hathaway A, Chiuzan C, Shirai K. Survival of melanoma patients with brain metastases treated with ipilimumab and stereotactic radiosurgery. Cancer Med. 2015;4(1):1–6.
80. Margolin K, Ernstoff MS, Hamid O, Lawrence D, McDermott D, Puzanov I, et al. Ipilimumab in patients with melanoma and brain metastases: an open-label, phase II trial. Lancet Oncol. 2012;13(5):459–65.
81. Specenier P. Nivolumab in melanoma. Expert Rev Anticancer Ther. 2016;16(12):1247–61.
82. Robert C, Schachter J, Long GV, Arance A, Grob JJ, Mortier L, et al. Pembrolizumab versus ipilimumab in advanced melanoma. N Engl J Med. 2015;372(26):2521–32.
83. Knisely JPS, Yu JB, Flanigan J, Sznol M, Kluger HM, Chiang VLS. Radiosurgery for melanoma brain metastases in the ipilimumab era and the possibility of longer survival. J Neurosurg. 2012;117(2):227–33.
84. Ahmed KA, Stallworth DG, Kim Y, Johnstone PA, Harrison LB, Caudell JJ, et al. Clinical outcomes of melanoma brain metastases treated with stereotactic radiation and anti-PD-1 therapy. Ann Oncol. 2016;27(3):434–41.
85. Tawbi HA, Forsyth PA, Algazi A, Hamid O, Hodi FS, Moschos SJ, et al. Combination nivolumab and ipilimumab in melanoma metastatic to the brain. N Engl J Med. 2018;379:722–30.
86. Long GV, Atkinson V, Lo S, Sandhu S, Guminski AD, Brown MP, et al. Combination nivolumab and ipilimumab or nivolumab alone in melanoma brain metastases: a multicenter randomised phase 2 study. Lancet Oncol. 2018;19(5):672–81.