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Targeted therapy of brain metastases: latest evidence and clinical implications

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Abstract: Brain metastases (BM) occur in 20–40% of patients with cancer and 60–75% of patients with BM become symptomatic. Due to an aging population and advances in the treatment of primary cancers, patients are living longer and are more likely to experience complications from BM. The diagnosis of BM drastically worsens long-term survival rates, with multiple metastases being a poor prognostic factor. Until recently, the mainstay of treatment consisted of stereotactic radiosurgery (SRS), surgical resection, whole brain radiation therapy (WBRT), or a combination of these modalities. Systemic chemotherapy has been felt largely ineffective in the treatment of BM due to the presence of the blood–brain barrier (BBB), which includes efflux pumps on brain capillaries. Over the past decade however, researchers have identified therapeutic agents that are able to cross the BBB. These findings could make a multimodality treatment approach possible, consisting of surgery, radiation, immunotherapy, and targeted therapy, which could lead to better disease control in this patient population and prolong survival. In this review, we discuss present evidence on available targeted therapies and their role in the treatment of BM from primary tumors with the highest prevalence of central nervous system (CNS) involvement, specifically non-small cell lung cancer (NSCLC), breast cancer melanoma, and renal cell carcinoma.

Keywords: brain metastases, targeted therapy

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Targeted therapies for brain metastases in lung cancer

Lung cancer is the second most commonly diagnosed cancer overall and the leading cause of cancer death in both men and women.[1] Studies show 13–44% of patients with lung cancer develop brain metastases (BM) during their disease course.[2–4] Although the cumulative incidence of BM is greater in small cell lung cancer compared with non-small cell lung cancer (NSCLC), most studies are focused on the treatment of metastases from NSCLC as it constitutes the vast majority (80–85%) of lung cancer cases.[5] Prognosis after diagnosis of BM in patients with NSCLC is poor, with a median overall survival (OS) of 4–5 months when treated with whole brain radiation therapy (WBRT).[6]

NSCLC comprises a heterogeneous group of cancers, the three major subtypes being squamous cell carcinoma, large cell carcinoma, and adenocarcinoma which account for close to 40% of all lung cancers.[7] Within NSCLC, and predominantly adenocarcinomas, several distinct molecular driver mutations have been identified which contribute to the tumor's prognosis and treatment response.

Mutation of the epidermal growth factor receptor (EGFR) increases the kinase activity of EGFR that promotes tumor-cell survival.[8] Mutant EGFR is found in 10–35% of NSCLC and has emerged as an important target for molecular therapy of NSCLC.[9,10]

Erlotinib and gefitinib are first-generation inhibitors of the tyrosine kinase domain of EGFR and are approved by the United States Food and Drug Administration (FDA) for the treatment of patients with metastatic NSCLC whose tumors

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harbor EGFR mutations. Both drugs have been subject to extensive evaluation in the treatment of BM from NSCLC. The response rate to EGFR tyrosine kinase inhibitors (EGFR TKIs) was found to be higher in EGFR-mutant tumors compared with their EGFR wildtype counterparts.[11–14] Besides having longer OS and progression-free survival (PFS), patients with EGFR-mutant NSCLC had significantly delayed progression of central nervous system (CNS) disease.[11,12,14,15] In addition to increasing the tumor's responsiveness to EGFR TKIs, EGFR mutations appear to make the tumor more sensitive to radiation therapy (RT).[12,13] However, it is important to note that most studies were either retrospective analyses of existing databases[12–15] or prospective studies evaluating efficacy of second-line erlotinib or gefitinib in patients that had previously been treated with RT or chemotherapy.[11,16–20] Two published phase II trials evaluated first-generation EGFR TKIs as first-line therapy in patients with BM from EGFR-mutant NSCLC.[21,22] As part of the inclusion criteria, none of the patients had received prior treatment with chemotherapy or RT. At time of enrollment, all patients in the first study had asymptomatic BM,[21] and only three (7.3%) patients in the second study had neurological deficits attributed to their BM.[22] Both studies showed favorable response of BM to either gefitinib or erlotinib with PFS of 14.5 months and 7.1 months, respectively, and OS of 21.9 months and 18.8 months, respectively. Both studies were conducted in patients of Asian ethnicity, a population found to have a high prevalence of EGFR mutations.[23] The frequency of EGFR mutations is lower in patients of non-Asian ethnicity.[24]

Preclinical studies demonstrated that EGFR TKIs enhance cytotoxic effects of radiation on NSCLC cells.[25,26] This finding was supported by two phase II clinical trials that found improved PFS and OS in RT-naïve patients with BM from EGFR-mutated NSCLC treated with WBRT combined with EGFR TKI, however, no clear benefit was seen in patients with wildtype EGFR NSCLC.[27,28]

Little data are available on the second-generation EGFR TKI afatinib, an irreversible EGFR inhibitor. As part of a compassionate use program, a prospective study was performed, assessing the efficacy of afatinib in 100 patients with NSCLC and CNS metastases.[29] All patients had failed at least one prior platinum-based chemotherapy and had progressive disease on a first-generation EGFR TKI. It was not mentioned whether patients had undergone prior RT for their BM. A sum of 74% of patients had an EGFR-mutant NSCLC. Time to tumor progression in patients with CNS metastases treated with afatinib was 3.6 months, overall cerebral response rate was 35%, and stable CNS disease (defined as no CNS disease progression while on afatinib treatment for >4 months) was seen in 39% of the evaluable patients. Further clinical trials on the efficacy of afatinib for the treatment of CNS metastases in patients with NSCLC are underway [ClinicalTrials.gov identifier: NCT02768337].

A third-generation EGFR TKI, osimertinib, has been approved for patients with a specific EGFR mutation who failed prior TKI treatment.[30] CNS penetration and activity of third-generation EGFR TKIs have been shown in clinical trials[31–34] and additional studies are ongoing [ClinicalTrials.gov identifiers: NCT02972333, NCT02736513, NCT02971501].

A small subset of about 3–7% of patients with NSCLC have an oncogenic fusion of two genes, the anaplastic lymphoma kinase (ALK) and echinoderm microtubule-associated protein-like 4 (EML4) gene.[35,36] These tumors are referred to as ALK-rearranged or ALK-positive NSCLC. While small, this subpopulation is of interest, as it is made up of mostly younger patients with little or no smoking history who tend to be resistant to EGFR TKI treatment.[36–39] Some data suggest that the prevalence of CNS metastases in patients with ALK-rearranged or EGFR-mutated NSCLC is higher (reported 25%)[40] than the 16–20% among unselected patients with NSCLC.[2,4] The first-generation ALK inhibitor, crizotinib, was approved by the FDA in 2011 for the treatment of patients with locally advanced or metastatic ALK-positive NSCLC. In an international phase III trial of 347 patients with locally advanced or metastatic ALK-positive NSCLC treated with either crizotinib or chemotherapy, PFS and response rates were significantly higher in the crizotinib arm (PROFILE 1007).[41] A retrospective analysis of PROFILE 1007 and the earlier PROFILE 1005[42] evaluated the intracranial response to crizotinib in patients with BM from ALK-positive NSCLC.[43] The authors specifically compared outcomes in patients who had received prior RT for their BM with treatment-naïve patients. Median time to progression of intracranial disease in the pretreated population was 13.2 months compared with 7.0 months in the

previously untreated group. Intracranial disease control rate was similar for both groups (56% in previously untreated and 62% in the RT-treated patients). In patients without BM at the time of crizotinib initiation who went on to develop progressive disease while receiving crizotinib, 20% were found to have BM. However, there are multiple reports of acquired resistance to crizotinib and resulting in progression of CNS disease.[44–48]

Two second-generation ALK TKIs, ceritinib and alectinib, have better CNS penetration and are approved for the treatment of patients with ALK-positive metastatic NSCLC who failed crizotinib.[49,50] An open-label phase I trial including 20 institutions in 11 countries assessed the safety and efficacy of ceritinib in 246 patients with ALK-rearranged NSCLC who had progressive or metastatic disease (ASCEND-1).[51,52] Outcomes were compared between ALK-inhibitor naïve patients (83 of 246, 34%) and those who had been previously treated with a first-generation ALK-inhibitor (163 of 246, 66%). Overall response to ceritinib, duration of response, and PFS were more favorable in the ALK-inhibitor naïve group. A total of 94 (38%) patients had retrospectively confirmed BM and at least one post-baseline magnetic resonance imaging (MRI) or computed tomography (CT) evaluation. With ceritinib therapy, intracranial response rate was 79% and 65% in ALK-inhibitor naïve and ALK-inhibitor pretreated patients, respectively. Intracranial response rate to ceritinib was similar for patients with prior RT to the brain or those who were RT naïve. Six of eleven patients with measurable CNS lesions had not received prior RT to the brain and demonstrated partial intracranial response to ceritinib. An open-label, multicenter phase II trial is ongoing to assess the efficacy and safety of ceritinib in patients with ALK-positive NSCLC who have metastases to the brain and leptomeninges [ClinicalTrials.gov identifier: NCT02336451].[53] This is a five-arm study that includes patients with and without prior treatment with the first-generation ALK-inhibitor crizotinib and with and without prior RT to the brain.

After safety and preliminary efficacy of alectinib in patients with ALK-positive NSCLC were established in a phase I trial,[54] a multi-center, single-group, open-label phase II trial was performed in North America.[55] All patients had ALK-positive NSCLC that was locally advanced or associated with metastatic disease, and had been treated with various regimens of RT, chemotherapy, and the first-generation ALK-inhibitor crizotinib prior to enrolment. Baseline brain imaging with MRI or CT was performed in all patients. Of 87 enrolled patients, 16 (18%) had measurable CNS disease at baseline, 11 (69%) of which had received prior RT to the brain. Complete CNS response was observed in 25% (4 of 16) of patients and partial response in 50% (8 of 16), accounting for an objective intracranial response of 75%. Median duration of CNS response was 11.1 months. A global phase II trial assessing 138 patients with ALK-positive NSCLC who had failed crizotinib and were treated with second-line alectinib showed similar results.[56] Of the 35 (25%) patients with measurable CNS metastases at baseline, 7 (20%) had a complete response, with an overall CNS response rate of 57%. CNS disease control rate was 83%, with a median duration of response of 10.3 months. Gadgeel and colleagues performed a pooled analysis of these two trials that combined 225 evaluated patients of whom 136 patients (60%) had CNS metastases at baseline, 50 patients with measurable CNS disease and 86 patients with nonmeasurable CNS disease.[57] All patients had received prior treatment with crizotinib and 95 patients (70%) had undergone RT prior to recruitment. CNS objective response rate was 42.6% (58 of 136 patients) with a complete response seen in 27.2%, partial response in 15.4%, and stable disease in 42.6% of patients. Median CNS duration of response was 11.1 months. Twelve patients (8.8%) had progressive disease. More studies are underway assessing the response of CNS metastases in patients with ALK-positive NSCLC to alectinib [ClinicalTrials.gov identifiers: NCT02075840, NCT02604342, NCT02521051].

Another second-generation ALK-inhibitor, brigatinib, has shown promising antitumor activity in patients with ALK-positive NSCLC and associated CNS disease.[58] This has been further confirmed by an ongoing multicenter, open-label, single-arm phase I/II trial that evaluated 79 patients with ALK-positive NSCLC [ClinicalTrials.gov identifier: NCT01449461]. A total of 22% (17 of 79) patients had documented measurable CNS metastases prior to brigatinib treatment. Of these, 15 of 17 had follow-up brain imaging that showed an intracranial response in 53% (8 of 15) patients.[59] A *post hoc* analysis of this study reported 49 patients had BM at baseline. According to the analysis, 87% of patients achieved intracranial disease control. A total of 45

patients (92%) had a median PFS of 22.3 months; OS or PFS of the remaining four patients were not reported.[60] A multicenter, open-label phase III trial is currently being conducted comparing brigatinib with crizotinib in the treatment of advanced ALK-positive NSCLC, looking at intracranial response rate and PFS, among other things [ClinicalTrials.gov identifier: NCT01449461]. There are further encouraging early clinical data that another ALK-inhibitor with CNS penetrance is an effective treatment option for patients with CNS metastases from ALK-positive NSCLC, and further studies are underway.[61–63]

Several other oncogenic driver mutations have been found in NSCLC such as ROS proto-oncogene 1, receptor tyrosine kinase (ROS1), proto-oncogene B-RAF (BRAF), RET proto-oncogene, human epidermal growth factor 2 (HER2) gene, mesenchymal-epithelial transition factor receptor tyrosine kinase gene (MET), and neurotrophic tyrosine receptor kinase (NTRK) gene.[64] Target agents for these gene mutations have been identified and are being studied for the treatment of patients with NSCLC, thus far with mixed results.[64] Except for one case report, we did not find data on the efficacy of a targeted approach to BM in patients with NSCLC with the above listed oncogenic mutations.

Targeted therapies for brain metastases in breast cancer

Breast cancer is the most common cancer in women and second most common cause of cancer death in women.[65] BM are found in 10–20% of breast cancer patients.[66,67] This number is even higher in autopsy studies of patients with breast cancer where prevalence of BM reaches 40%.[68,69] The current standard of care for the treatment of BM from breast cancer consists of either surgical resection, SRS, or WBRT.

Different criteria have been used for the classification of breast cancers, for example, World Health Organization grading, histopathological appearance, hormone receptor status, and few others. For the purpose of this review, we focused on the subtypes based on hormone and growth factor receptor status [estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 (HER2)].

Approximately 25–30% of patients with breast cancer have overexpression of the HER2.[70,71] HER2-enriched breast cancers are 2–4 times more likely to spread to the CNS, and 30–50% of patients with HER2-enriched breast cancers will develop BM.[72–74]

Trastuzumab is a monoclonal humanized antibody directed against the extracellular domain of HER2 and approved for the treatment of HER2-positive breast cancer. Several clinical trials have shown great efficacy of HER2-monoclonal antibodies with regards to systemic disease control as well as OS and PFS of patients with HER2-positive breast cancer.[75–77] Trastuzumab cannot cross the intact BBB due to its large molecular size that may result in relapse, as seen in metastatic CNS disease.[73,78] However, clinical studies using positron emission tomography (PET) showed BM uptake of radiolabeled trastuzumab, suggesting that the BBB surrounding BM is not intact, allowing trastuzumab pene-tration.[79,80] Retrospective studies have suggested that CNS metastases can respond to intravenous trastuzumab.[81] Although prospective data are lacking at this time, prospective clinical trials are in progress, assessing the efficacy of trastuzumab in the treatment of BM in patients with HER2-positive breast cancer [ClinicalTrials.gov identifiers: NCT02598427, NCT02571530, NCT01325207].

Lapatinib is a small tyrosine inhibitor that interferes with HER2 and EGFR signaling, therefore leading to dual inhibition of both pathways.[82] Lapatinib is believed to cross the BBB more easily due to its small molecular size, however its CNS availability and concentration is limited by cancer resistance protein and efflux pumps.[83] An open-label, multicenter phase II trial enrolled 242 patients with BM from HER2-positive breast cancer who had been treated with trastuzumab and either WBRT (95%), SRS (26%), or both (21%), and had subsequently received lapatinib.[84] CNS objective response rate was 6%, all were partial responses. Stable disease was seen in 37% and progressive disease in 46%; OS and PFS were 6.4 and 2.4 months, respectively. Fifty patients entered an extension phase of the trial and received additional treatment with combination of lapatinib plus capecitabine. Among these patients, the objective CNS response rate (all partial responses) was 20% and median PFS was 3.7 months. The LANDSCAPE trial was an open-label, multicenter phase II trial that evaluated the response of previously untreated CNS metastases from HER2-positive breast cancer to first-line

lapatinib–capecitabine combination therapy in radiation-naïve patients.[85] A total of 45 patients were enrolled, of which 42 (93%) had received prior treatment with trastuzumab. Objective CNS response was seen in 29 (66%) patients, all partial responses. Median OS was 17 months, with an OS at 6 months of 90.9%. Median time to disease and CNS progression was 5.5 months. This treatment regimen deferred the need for WBRT for a median of 8.3 months. An ongoing phase II trial is investigating the efficacy of lapatinib in combination with RT in the treatment of BM from HER2-positive breast cancer [ClinicalTrials.gov identifiers: NCT00470847, NCT01622868].

Trastuzumab emtansine (T-DM1), an antibody–drug conjugate of trastuzumab and the cytotoxic microtubule–inhibitor DM1 (also known as mertansine, emtansine, or derivative of maytansine), was approved by the FDA for the treatment of patients with metastatic HER2-positive breast cancer. Approval was based on the phase III EMILIA trial, that compared T-DM1 with lapatinib plus capecitabine for the treatment of advanced HER2-positive breast cancer.[86] Patients treated with T-DM1 had longer PFS (9.6 months *versus* 6.4 months), median OS (30.9 months *versus* 25.1 months), and objective response rate (43.6% *versus* 30.8%) compared with the lapatinib–capecitabine group. A subsequent retrospective review of the EMILIA trial looked at the response of CNS metastases in both treatment arms.[87] Patients diagnosed with CNS metastases before treatment initiation had a significantly longer OS if treated with T-DM1 (26.8 months *versus* 12.9 months in the lapatinib–capecitabine treatment group). PFS of patients with baseline CNS metastases was similar in both groups. Bartsch and colleagues looked at 10 patients with asymptomatic or progressive BM from HER2-positive breast cancer who received T-DM1 as primary systemic treatment for their BM.[88] All patients had previously been treated with trastuzumab, as well as lapatinib (6 of 10 patients) or pertuzumab (3 of 10 patients) for their extracranial disease. CNS clinical benefit, defined as complete response, partial response, or stable disease was reported in 50% (5 of 10) of patients.

Other agents being investigated for the treatment of CNS metastases from HER2-positive breast cancer include afatinib and neratinib, two dual inhibitors of HER2 and EGFR transmembrane tyrosine kinases. A multicenter, open-label phase II trial assessed the response of recurrent or progressive BM in patients with HER2-positive breast cancer to either afatinib alone, afatinib plus vinorelbine, or an investigator's choice of treatment.[89] All patients had received prior treatment with trastuzumab, lapatinib, or both for their primary tumor, as well as either prior RT, systemic therapy, or both for CNS metastases. Previous treatment modalities were well balanced across the different treatment groups. Patient benefit at 12 weeks, defined as no CNS or extra-CNS disease progression, absence of tumor-related worsening of neurological symptoms, and no increase in steroid dose, did not differ between the three treatment groups. Intracranial disease control was achieved in 27 of 40 (68%) patients in the afatinib-only group, 27 of 38 (71%) in the afatinib plus vinorelbine group, and 31 of 43 (72%) in the investigator's choice treatment group. Neratinib was studied in another open-label phase II trial that assessed its efficacy in the treatment of BM from HER2-positive breast cancer.[90] Forty patients were recruited, all of whom had previously failed CNS-directed therapy including SRS, surgery, WBRT, or any combination. The majority of patients had received prior systemic treatment for their extra-cranial disease, mainly with trastuzumab or lapatinib. No complete CNS response was seen, 3 of 40 (8%) patients had a partial CNS response and 16 patients (40%) achieved stable CNS disease. Median time to disease progression was 1.9 months and OS was 8.7 months. This study also examined neurocognitive function and quality of life before and after treatment, both of which were worse after treatment, a result that is not surprising considering that many of these patients had also undergone prior WBRT, which is known to negatively impact cognitive function.

A comparatively small percentage, about 5%, of patients with luminal, estrogen receptor (ER)-positive breast cancer develop BM.[91] It was found that a significant fraction of ER-positive breast cancers undergo conversion of their hormone receptor status, leading to ER-negative CNS metastases.[92] Thus far, only anecdotal data from case reports suggest a benefit of continued hormonal therapy with tamoxifen or megestrol acetate for the treatment of BM.[93–95]

Agents inhibiting the action of the mechanistic target of rapamycin (mTOR), a regulator of cell metabolism and proliferation, and cyclin-dependent kinase 4 and 6 (CDK4, CDK6), which are associated with tumorigenesis, have shown

activity for extracranial manifestations of luminal breast cancer with no reports on their effect on BM.[96,97]

Triple-negative breast cancers lacking expression of hormone (estrogen or progesterone) and HER2-receptors are associated with an increased risk of BM compared with hormone-receptor-positive breast cancers.[98,99] There is an urgent need for good treatment options for patients with BM from triple-negative breast cancer.

Targeted therapies for brain metastases in melanoma

Nearly 50% of patients with advanced malignant melanoma develop BM, and the prevalence of BM in autopsies of these patients is even higher, at 75%.[100–102] Multiple BM in malignant melanoma is associated with a poor prognosis, and survival of these patients is generally 6 months or less following diagnosis.[103,104] Historically, WBRT is less utilized in this patient population as the tumor is considered radiation-resistant.[105–107] SRS has been the preferred treatment choice, even for multiple BM, though associated with a high rate of local recurrence.[108–110] Patients with BM from malignant melanoma are frequently found to have multiple small metastases, which makes systemic therapy, if effective, a viable treatment option.

The proto-oncogene B-RAF, a gene encoding the growth signal transduction protein kinase BRAF, is mutated in approximately 50% of malignant melanomas.[111] B-RAF is part of the so-called Ras-Raf-MEK-MAPK pathway that regulates gene transcription and mRNA translation. A mutation of B-RAF (or BRAF) causes a substitution at codon 600 of the amino acid valine (V) to glutamate (E) in over 90% of cases, and to lysine (K) in 5% of cases, which lead to the $BRAF^{V600E}$-mutant and $BRAF^{V600K}$-mutant, respectively. BRAF-mutant melanoma has been shown associated with a higher prevalence of CNS involvement compared with wild type (24% *versus* 12%).[112] Currently, two mutant BRAF-inhibitors are approved by the FDA for the treatment of advanced malignant melanoma: vemurafenib and dabrafenib have undergone clinical investigation in brain metastases. Phase III trials have shown longer OS and PFS in patients treated with either vemurafenib or dabrafenib compared with patients who received dacarbazine, a chemotherapeutic agent widely used in the treatment of advanced melanoma.[113,114]

In an open-label, pilot phase II trial, 24 patients with nonresectable, previously treated BM from malignant melanoma received vemurafenib for their BM.[115] Median PFS was 3.9 months and median OS was 5.3 months. A total of 7 of 19 patients (37%) with measurable intracranial disease at baseline experienced intracranial tumor regression of >30%, with 3 patients (16%) showing partial intracranial response and 13 (68%) showing stable intracranial disease. Several retrospective reviews looked at the intracranial response rate (RR) in patients treated with vemurafenib for BM from BRAF-mutant melanoma and reported an intracranial RR of 50%, OS of 30–59% at 12 months and median PFS of 4.1 months.[116–118] A recent multicenter, open-label phase II trial assessed the response of BM from BRAF-mutated melanoma to vemurafenib.[119] The study was divided into two cohorts: cohort 1 compromising 90 patients with previously untreated BM, and cohort 2 consisting of 56 patients who had received prior treatment for their BM. Overall best intracranial RR was seen in 16 of 90 patients (18%) in cohort 1, with two patients experiencing complete response and 14 patients having partial response. Intracranial RR was not reported for cohort 2. Overall best combined (intracranial and extracranial) RR was 19% in cohort 1 and 18% in cohort 2. Duration of intracranial response was reported to be 4.6 months in cohort 1 and 6.6 months in cohort 2. Median OS and PFS were 8.9 months and 3.7 months in cohort 1, respectively, and 9.6 months and 4.0 months in cohort 2, respectively. In a retrospective review of 86 patients with malignant melanoma without initial CNS involvement, 17 of 86 patients (20%) developed new BM while receiving treatment with vemurafenib.[120] Extracranial disease was stable in 59% of patients who had new CNS involvement, suggesting the CNS to be a frequent site of relapse in this patient population.

Preliminary safety and efficacy data for dabrafenib in melanoma BM was noted in a phase I trial that included 10 patients with asymptomatic, untreated BM.[121] A total of 9 of 10 patients (90%) had a decrease in size of BM, and 4 of 10 (40%) were found to have complete resolution of BM. Median PFS was 4.2 months. This study was followed by a multicenter, open-label phase II trial that enrolled 172 patients with BM from malignant melanoma who underwent treatment with dabrafenib.[122] The study included two cohorts, patients with previously untreated BM (cohort A, 89 patients, 52%) and patients who had received

prior local treatment for their BM (cohort B, 83 patients, 48%). Both cohorts were further divided according to their BRAF-mutation subtype, $BRAF^{V600E}$-mutant or $BRAF^{V600K}$-mutant. Among the 74 patients in cohort A with untreated BM and $BRAF^{V600E}$-mutant melanoma, 29 patients (39.2%) achieved an overall intracranial response. In cohort B, the overall intracranial response to dabrafenib among patients with $BRAF^{V600E}$-mutant melanoma was 30.8% (20 of 65 patients). PFS and OS were 16.1 months and 33.1 months for cohort A, respectively, and 16.6 months and 31.4 months in cohort B, respectively. Response rates were lower for patients with $BRAF^{V600K}$-mutant melanoma, with only 1 of 15 patients (6.7%) in cohort A and 4 of 18 (22.2%) in cohort B showing an intracranial response to dabrafenib. Similarly, PFS and OS were shorter in $BRAF^{V600K}$-mutant group, with a PFS and OS of 8.1 months and 16.3 months in cohort A, respectively, and 15.9 months and 21.9 months in cohort B, respectively. Therefore, while having limited efficacy in $BRAF^{V600K}$-mutant melanoma, dabrafenib appears to show good activity against BM in patients with $BRAF^{V600E}$-mutant melanoma.

A significant challenge arising from the treatment of melanoma with BRAF-inhibitors is the development of resistance to BRAF inhibition, as well as the development of secondary skin tumors, specifically squamous cell carcinomas. BRAF-inhibitors can lead to paradoxical BRAF-inhibitor resistance by upregulating the activity of other RAF kinases involved in the Ras-Raf-MEK-MAPK pathway, such as A-RAF or C-RAF, which lead to reactivation of the Ras-Raf-MEK-MAPK pathway and therefore to increased transcription and tumor cell proliferation.[123–127]

An open-label phase III trial assessed the efficacy of combination treatment with the BRAF-inhibitor dabrafenib and the MEK-inhibitor trametinib in patients with metastatic melanoma. MEK stands for the mitogen-activated protein kinase and is also part of the Ras-Raf-MEK-MAPK transcription pathway. The study showed that dabrafenib plus trametinib was superior to vemurafenib monotherapy for the treatment of metastatic melanoma, leading to an improved 12 months OS (72% *versus* 65%) and longer median PFS (11.4 months *versus* 7.3 months).[128] The COMBI-MB trial is a multicenter, open-label, phase II trial that assessed intracranial response to combination treatment with dabrafenib and trametinib in patients with BM from BRAF-mutated melanoma.[129] The study population was divided into four cohorts based on BRAF mutant, symptomatology of BM, previous local brain therapy, and Eastern Cooperative Oncology Group (ECOG) performance status. The study was designed to detect a treatment response in patients with $BRAF^{V600E}$-mutant, asymptomatic BM, no prior local brain therapy, and ECOG performance status of 1 or less (cohort A). An OS and PFS of 10.8 months and 5.6 months, respectively, and a 6-month OS and PFS rate of 79% and 44%, respectively, were observed in this cohort. The other three cohorts were defined as follows: Cohort B: patients with $BRAF^{V600E}$-mutant, asymptomatic BM, prior local brain therapy, and ECOG performance status of 1 or less; cohort C: patients with $BRAF^{V600D/K/R}$-mutant, asymptomatic BM, with or without prior local brain therapy, and ECOG performance status of 1 or less; cohort D: patients with $BRAF^{V600D/E/K/R}$-mutant, symptomatic BM, with or without prior local brain therapy, and ECOG performance status of 2 or less. Intracranial responses were also seen in cohorts B, C and D but were considered exploratory findings based on the small sample sizes. Compared with historical controls, patients appeared to benefit clinically from dabrafenib plus trametinib treatment that led to a median OS of 10.1–24.3 months *versus* 3.4 months with WBRT alone.[129]

Another focus of ongoing research is the safety and efficacy of combined RT and BRAF-inhibitors for the treatment of BM from BRAF-mutated melanoma. This topic has been of interest since early preclinical studies suggested that BRAF-inhibitors reversed the radioresistance of BRAF-mutated melanoma cells.[130] Several retrospective clinical studies confirmed that adding BRAF-inhibitors to SRS to treat BM from malignant melanoma was generally safe and improved OS and intracranial disease control.[131–136] Unfortunately, the amplified effect of RT by BRAF-inhibitors was not limited to tumor cells but also led to high rates of dermatological toxicities and intracranial hemorrhages.[134,137–139] Weighing the risks and benefits of combined RT and BRAF-inhibitor treatment will likely remain a challenge until results from prospective trials are available.

Targeted therapies for brain metastases in renal cell carcinoma

The yearly incidence of cancer of the kidneys and renal pelvis accounts for approximately 4–5%

among all cancers, the vast majority being renal cell carcinoma (RCC).[140] BM occur in 2–10% of patients with RCC and are usually found within the first year of primary tumor diagnosis.[2,66] Median survival of patients with metastatic RCC is often <1 year,[141–143] and as low as 4 months in patients that present with BM.[144] Surgical resection, which is often curative for localized tumors, tends to be insufficient in patients with metastatic RCC.

Sunitinib is a multitarget receptor tyrosine inhibitor that reduces tumor angiogenesis and cell growth by inhibiting vascular EGFR and platelet-derived growth factor receptors. First-line treatment with sunitinib has been shown to significantly prolong OS and PFS in patients with metastatic RCC compared with interferon alpha.[145,146] Anecdotal data from retrospective studies and case reports suggest that sunitinib is safe and effective in the treatment of BM from RCC.[147–149] Prospective data on the efficacy of sunitinib for the treatment of BM from RCC include a multicenter, single-arm phase II trial performed in France.[150] A total of 17 patients with RCC and asymptomatic, measurable and inoperable BM were treated with sunitinib. Of these, 16 of the initial 17 patient were available for evaluation following completion of sunitinib treatment. None of the patients had an objective response of intracranial disease. Stable CNS disease was seen in five patients (31%), with a median time to progression of 2.3 months and median OS of 6.3 months. Results of another phase II trial looking at the efficacy of sunitinib used to treat BM in patients with RCC are pending [ClinicalTrials.gov identifier: NCT00462982].

Case reports suggest that pazopanib, another multikinase inhibitor, may be efficacious in the treatment of BM from RCC but requires confirmation by prospective trials.[151–153]

Immunotherapy

Immunotherapy is a treatment approach that supports the immune system's ability to fight cancer, either by stimulating it or by providing components that enhance its activity. The immune system is equipped with cell surface receptors which downregulate the immune response to certain antigens and thereby promote tolerance. These receptors are commonly referred to as immune checkpoints. While preventing an immune overreaction to harmless antigens, these receptors also inhibit the intrinsic immune response directed towards cancer cells. Inhibitors of these receptors, so-called checkpoint inhibitors, are being progressively used for the treatment of certain cancers. Ipilimumab is a monoclonal antibody that targets the immune checkpoint cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and is approved for the treatment of unresectable and metastatic melanoma.[154] Another checkpoint inhibitor, the monoclonal antibody nivolumab, is directed against immunoglobulin G4 (IgG4) and the programmed cell-death protein 1 (PD-1), and approved for the treatment of patients with unresectable or metastatic melanoma, disease progression following ipilimumab therapy, as well as for the treatment of patients with BRAF-mutated melanoma previously treated with a BRAF-inhibitor.[155–157] The CNS has long been considered an immune privileged site, however in recent years this has been found not to be the case. A phase II study of ipilimumab showed efficacy in the treatment of patients with BM from melanoma.[158] A phase II study with pembrolizumab demonstrated 33 % and 22% response rate in lung cancer and melanoma BM, respectively.[158] More recently, two trials presented at ASCO 2017, showed activity of combined nivolumab and ipilimumab against asymptomatic BM in melanoma patients.[159,160]

Conclusion

Targeted therapies have demonstrated a significant impact on the disease control, survival, and quality of life in patients with advanced cancer. Data on the safety and efficacy of targeted therapies in the treatment of CNS manifestations of primary extracranial cancers are comparatively limited, though overall promising, especially with the advent of newer agents that have better BBB penetration. Studying efficacy of targeted therapies for BM has several challenges. Most trials on dosing, safety and efficacy of initial targeted treatments generally have excluded patients with BM. The BBB is often the first obstacle to efficacy, by its prevention of drugs from reaching the target tissue. On the other hand, as previously discussed, the BBB surrounding BM appears to be defective, allowing penetration of certain drugs. The degree of permeability may vary depending on the size and location of BM, making it difficult to calculate the required dose. Performing routine stereotactic brain biopsies solely for the purpose of histological analysis, and drug concentration

studies to determine dose–response rates is not feasible for obvious reasons. Until recently, most agents were evaluated after patients had failed prior radiation and this is a poor-outcome population. A number of trials are now evaluating these drugs prior to radiation.

There are currently no established response criteria for intracranial metastases. The Response Assessment in Neuro-Oncology Brain Metastases (RANO-BM) criteria have been proposed but need validation in studies. A number of trials have used different criteria to define success, making it difficult to compare the results.

Researchers and clinicians face many challenges when designing and conducting studies for cancer patients with BM. However, encouraging progress has been made in recent years regarding targeted therapies for BM from selected primary cancers. We are hopeful that the continued search for drugs that reach and treat BM will eventually help patients extend survival and increase their quality of life.

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Conflict of interest statement

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