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Review

New developments in brain metastases

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***Abstract*:** Patients with brain metastases (BM) are a population of high clinical need for new therapeutic approaches due to, as yet, very impaired survival prognosis. However, only few clinical trials have specifically addressed this prognostically highly heterogeneous patient population. New developments in the treatment of BM patients aim to reduce the side effects of local therapies, for example, by redefining the indications for stereotactic radiosurgery and whole-brain radiotherapy (WBRT) or introducing new applications like hippocampal sparing WBRT. Furthermore, systemic therapies become a more important treatment approach in patients harboring targetable mutations, as recent BM-specific endpoints in several phase III trials have shown promising intracranial efficacy. In addition, immune-checkpoint inhibitors show promising intracranial efficacy, particularly in patients with melanoma and non-small lung cancer BM. Here, we provide a review on the recent new developments in the local and systemic therapy approaches in BM patients.

Keywords: ALK translocation, anti-HER2 therapy, brain metastases, EGFR mutation, immune-checkpoint inhibitors, targeted therapies

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Introduction

Brain metastases (BM) are a frequent complication in patients with metastatic cancer and pose a particular treatment challenge, as both the intracranial, and extracranial disease need to be treated; moreover, the patient's symptoms need to be managed.[1] Survival prognosis differs dramatically between disease entities: for example, long-term survival over 2 years can be observed in patients with BM from HER2 positive breast cancer, whereas median survival prognosis in other entities such as nonmutated non-small cell lung cancer (NSCLC) is limited to approximately 1 year even in young patients with good Karnofsky performance score.[2] Therefore, treatment algorithms should consider the histology of the primary tumor, including possible target mutations, as well as clinical characteristics like age of the patients, Karnofsky performance score, number of BM, and the activity of the extracranial disease.[3] Optimal patient selection based on the estimated survival prognosis is crucial to avoid unnecessary toxicity in patients with poor prognosis, and late complications in patients with favorable prognosis, and to facilitate a personalized treatment approach in this particular patient population with high medical need.[4,5]

Local therapies such as stereotactic radiosurgery (SRS), neurosurgical resection and whole brain radiotherapy (WBRT) remain the main treatment approaches for symptomatic BM.[3] Recent trials have focused on new methods, including hippocampal sparing WBRT, or new combinations like postsurgical SRS of the resection cavity, or application of SRS to multiple (up to 10) BM to reduce the neurological side effects by maintaining the intracranial disease control.[6,7] Furthermore, systemic therapies became a more important part of BM treatment, especially in patients with asymptomatic or oligosymptomatic disease.[3] Recent phase III trials allowed the inclusion of BM patients and the conduction of BM-specific trials has further extended the knowledge on the efficacy of systemic therapies in BM patients. In this review, we will provide a comprehensive overview on the recent new treatment developments in local and systemic therapies of BM patients.

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New developments in local therapies for brain metastases

Local therapies are the backbone of treatment, especially for patients with symptomatic BM as immediate symptom relief is needed.[3,8,9] The type of local therapy is based mostly on the number and size of the BM. Patients with up to three BM with a diameter less than 3 cm are, as a rule, most frequently treated with SRS; whereas patients with multiple BM are rather treated with WBRT.[3] However, SRS is increasingly considered for multiple BM with the goal of limiting brain tissue exposure to radiation.

New developments in the indication and application of whole brain radiotherapy

Given the neurotoxicity and neurocognitive side effects, the application of WBRT is controversial and critically discussed, and several recent studies on new developments in the local treatment of BM focus on redefining the indications and application methods of WBRT.[10] A multi-institutional prospective observational study recently postulated that SRS, which causes less neurocognitive side effects than WBRT, could also be applied in patients with up to 10 BM. The benefit from the localized treatment with SRS on overall survival (OS) was not inferior to patients treated for only two to four BM.[7] WBRT-associated side effects, including leukoencephalopathy or deterioration of neurocognitive function, were only infrequently observed in the cohort, further supporting the non-inferiority of SRS alone compared with WBRT in patients with up to 10 BM.[11] Considering the minimal invasiveness of SRS, the possibility of also applying localized high radiation to metastases that appear radioresistant on the basis of histology (e.g. those from melanoma) and the favorable side-effect profile compared with WBRT, SRS might indeed be a suitable treatment option in selected patients with multiple, small BM and favorable survival prognosis (Karnofsky performance score > 70).

The recently published QUARTZ trial focused on the local therapy of patients with multiple BM and compared WBRT *versus* palliative care alone (including dexamethasone therapy) in patients with multiple NSCLC BM.[12] Although, per definition, the non-inferiority margin of palliative care alone compared with WBRT was not met, the combination of only a small difference in the quality-adjusted life years (QALYs; 46.4 QALY days in the WBRT *versus* 41.7 QALY days in the palliative care alone group) and a lack of difference in survival [hazard ratio (HR) 1.06; $p = 0.808$] might suggest that the omission of WBRT should be considered in selected patients, especially those with poor prognosis and asymptomatic BM.[10,12]

A further important new development in the local treatment of BM is the development of a WBRT method that spares the hippocampus, as the destruction of hippocampal neurons is postulated as the main cause of neurocognitive decline and side effects after WBRT.[6] Importantly, BM are almost never observed in the region of the hippocampus; therefore, selective avoidance of this vulnerable region is likely to not result in a higher rate of intracranial recurrence.[13] First studies proved the feasibility and safety of this new WBRT regimen and showed that neurocognitive functional preservation is indeed achieved of by hippocampal sparing during WBRT.[14,15]

Additional WBRT after resection or SRS of BM is a further controversially discussed indication. The prospective EORTC 22952–26001 trial investigated adjuvant WBRT *versus* observation after SRS or neurosurgical resection in patients with up three BM. No significant difference in time-to-performance-status deterioration between the groups was observed, whereas a significant decline in the quality of life was observed in the WBRT group.[16,17] However, local as well as distant brain relapse was numerically less frequently observed in patients with combined neurosurgical/SRS and WBRT approach, arguing that additional radiotherapy of the resection cavity might improve outcome. The NCCTG/N107C/CEC3 trial compared WBRT *versus* postoperative SRS of the resection cavity in patients with one resected BM. Survival time with no cognitive deterioration was significantly longer in the SRS than in the WBRT group (HR 0.47; $p < 0.0001$), whereas no difference in OS was observed (HR 1.07; $p = 0.70$), indicating that SRS should be considered one of the standard treatment options and as a less toxic alternative to additive WBRT after resection of a single BM.[18]

New development in the local treatment of brain metastases patients harboring targetable mutations

A further new development and a controversial topic in the local therapy of BM is the treatment algorithm for patients with multiple, oligo- to asymptomatic BM in the presence of a

targetable mutation, offering an effective systemic, brain-penetrant therapy.[3] Taking into account the side effects of WBRT which reduce quality of life, several studies addressed the question, and whether it is safe to postpone WBRT in this particular patient population and start with a systemic therapy as a first-line treatment approach.[3,4,19,20] As outlined in the following paragraphs on new developments in systemic therapies, several clinical prospective trials demonstrated the intracranial efficacy of targeted therapies as a monotherapeutic approach in patients with newly diagnosed oligo- to asymptomatic BM. However, prospective head-to-head comparison addressing this important issue, considering the potential long-term side effects, especially of WBRT, are rare. A single-center study comparing SRS plus upfront chemotherapy *versus* upfront chemotherapy alone revealed no survival benefit by the addition of SRS in patients with asymptomatic NSCLC BM (14.6 *versus* 15.3; $p = 0.418$).[21] However, these results have to be interpreted with caution, as the study was terminated early and results warrant verification in a larger prospective trial.

New developments in combining radiation and immune-checkpoint inhibitors

Combination of SRS with immune-checkpoint inhibitors is another emerging development in the treatment of BM patients. In theory, SRS could improve the response to immune-checkpoint inhibitors given that SRS results in an increased release of tumor antigen and has favorable impact on the composition of the inflammatory microenvironment.[22] The 'abscopal effect', defined as the response of distant lesions after radiation of a progressing lesion during the concomitant treatment with an immune-checkpoint inhibitor is a unique phenomenon that further supports the combination of immune-checkpoint inhibitors and SRS, especially in patients with BM, as SRS is frequently applied.[23] First promising data suggest that the 'abscopal effect' can be observed in patients treated with SRS for progressing BM, in combination with ipilimumab.[24] Several retrospective case series have shown the safety of continuing immune-checkpoint inhibitor therapy during SRS, and prospective studies are currently investigating the optimal timing, sequencing and SRS dosing in combination with immune-checkpoint inhibitors.[25,26]

New developments in systemic therapies of brain metastases

Approximately 20% of BM patients are diagnosed with asymptomatic or oligosymptomatic BM and, given the higher availability of computed tomography and magnetic resonance tomography (MRT) scanners as well as the inclusion of baseline BM screening in several guidelines, this percentage is likely to further increase in coming years.[1,27] Survival with an asymptomatic or oligosymptomatic BM can potentially be longer than with symptomatic BM, and the neurotoxic, quality-of-life-impairing side effects of radiotherapy, such as neurocognitive decline after WBRT or symptomatic radionecrosis after SRS, have to be considered in the therapeutic approach.[21,28] Most BM-specific trials were conducted in symptomatic patients in need of immediate neurological symptom relief, whereas in patients with asymptomatic or oligosymptomatic BM, the symptoms requiring treatment are likely to be extracranial. Therefore, a first-line systemic therapy approach has been recently introduced in selected patients with asymptomatic or oligosymptomatic BM.[3]

Chemotherapy regimens have shown only minor intracranial efficacy in patients suffering from BM. Most chemotherapy compounds have limited brain penetration due to the tight junctions of the blood–brain barrier that limit the therapeutically efficient diffusion into the brain parenchyma.[29] However, the blood–brain barrier is disrupted in the contrast-enhancing parts and might be replaced by a blood–tumor barrier, characterized by a higher fenestration of the endothelium and a resulting higher efflux of fluid, causing the characteristic peritumoral brain edema.[30] Other areas of the BM such as the invasion zone or noncontrast-enhancing areas without intensive neo-angiogenesis might still be in part protected by the blood–brain barrier, causing a very heterogeneous concentration of chemotherapeutic agents in BM and the resulting limited clinical efficacy.[31] Chemotherapies with a better brain penetration like, for example, the alkylating agent temozolomide, a standard medication in the therapy of primary brain tumors, have frequently only limited efficacy in histologies causing BM, such as NSCLC, breast cancer or melanoma and consequently, have no clinically relevant therapeutic efficiency as a monotherapy in BM patients despite their good brain diffusion characteristics.[32]

New targeted and immunomodulatory therapies were shown to have a higher extracranial therapeutic efficacy compared with chemotherapy in several frequently BM-causing entities and recently, also, a clinically relevant intracranial response rate was reported for several new compounds.[33] Tyrosine kinase inhibitors are small molecules allowing them to evenly diffuse *via* an intact blood–brain barrier, although diffusion of some is restricted by their affinity to efflux pumps like P-glycoprotein.[34] Most tyrosine kinase inhibitors have a mutation-specific function, resulting in limited efficacy in the absence of the predictive genetic alteration, and presence of the targeted mutation in the BM tissue is also a precondition for intracranial efficacy.[35] However, due to the clonal evolution, targeted mutations can be altered or lost and therefore differ between sites, resulting in a heterogeneous response pattern.[35,36] Brain biopsy or mutation-specific positron-emission-tomography imaging to evaluate the presence of targeted mutations might be used to validate the presence of a therapeutically, predictive mutation.[4,37] Several mutations, for example, the *v-Raf murine sarcoma viral oncogene homolog B* (*BRAF*) V600E mutation in melanoma or the *ALK* translocation in NSCLC were shown to present as rather stable between the sites, whereas others, including the overexpression of *HER2* in breast cancer, were shown to present with a variability between primary tumor and matched BM[38–40] (reviewed in Berghoff *et al*.[35]). Immune-checkpoint inhibitors reveal their efficacy in the regional lymph node, enhancing the tumor-specific T-cell response and activated T cells can cross even an intact blood–brain barrier. Furthermore, immune-checkpoint inhibitors specifically target immune inhibitory pathways upregulated in the tumor inflammatory microenvironment like programmed cell-death ligand 1(PD-L1), which was also shown to be upregulated in BM and thereby provide a promising treatment option even for intracranial malignancies.[41–44] Unfortunately, several phase III trials on new targeted and immune-modulating therapies systematically excluded BM patients resulting in only limited knowledge for intracranial efficacy for some compounds.[4] In the following paragraphs, we give an overview on the efficacy of systemic monotherapies (Table 1) for patients with asymptomatic BM in the most frequent BM-causing entities: NSCLC, breast cancer and melanoma.

Systemic therapies in non-small cell lung cancer brain metastases

Presence of predictive genetic alterations including the epidermal growth factor receptor *(EGFR)* gene mutation, *ALK* or *ROS1* translocation or *BRAF* V600E mutations as well as expression of PD-L1 in over 50% (in first-line palliative treatment) of the tumor tissue is the basement for systemic treatment decisions in metastatic NSCLC.[52]

The most frequent genetic alteration is an activating mutation in *EGFR*, which can be found in 10–15% of the population with a higher incidence in women, never-smokers and patients of east Asian ethnicity. Exon 19 deletion is the most frequently observed mutation type, followed by exon 21 point mutations, which are both established predictive biomarkers for the response to an EGFR tyrosine kinase inhibitors.[45,53,54] Exon 18 point mutation and exon 20 insert mutations are observed less frequently and are associated with a decreased response to EGFR tyrosine kinase inhibitors compared with the more frequent exon 19 and 21 alterations.[55]

Three generations of EGFR tyrosine kinase inhibitors have been established and are associated with higher response rates as well as longer progression-free survival and OS in patients with metastatic *EGFR*-mutated NSCLC compared with standard chemotherapy. Phase III studies of the first-generation EGFR tyrosine kinase inhibitors gefitinib and erlotinib mostly excluded patients with BM; however, more recent investigation postulated intracranial response in patients with asymptomatic BM (intracranial response rate 73.9%; OS 18.8 months) as well as the safety of combination with WBRT (intracranial response rate 86%; OS 11.8 months).[56,57] Second-generation EGFR tyrosine kinase inhibitor afatinib was shown to have a better extracranial response rate compared with first-generation EGFR inhibitors, especially in patients with exon 19 deletion; however, only limited data on the intracranial efficacy are available.[58] *Post hoc* analysis of the combined data of the LUX-LUNG 3 and LUX-LUNG 6 data suggested that patients with asymptomatic BM at baseline have a similar magnitude of progression-free survival improvement from afatinib therapy as patients without BM. In both trials, progression-free survival of BM patients treated with afatinib was longer, although not statistically significant, than in patients treated with first-line chemotherapy [LUX 3 (11.2 *versus* 5.4 months; $p = 0.14$),

Table 1. Selected trials on intracranial activity of targeted therapies as first-line monotherapy in asymptomatic to oligosymptomatic patients.

Tumor entity	Phase	Study design	BM endpoint	Reference
EGFR-mutated NSCLC	Phase III	Osimertinib *versus* first-generation EGFR tyrosine kinase inhibitor	PFS: 15.2 *versus* 9.6 months (HR 0.47; $p < 0.001$)	[45]
ALK-mutated NSCLC	Phase III	Alectinib *versus* crizotinib	PFS: 14.0 *versus* 7.2 months (HR 0.44; $p < 0.001$)	[46, 47]
NSCLC	Phase II	Single arm: pembrolizumab	ICR: 33%	[48]
HER2-overexpressing breast cancer	Phase II	Single arm: capecitabine + lapatinib	PFS: 8.3 months	[19]
BRAF-mutated melanoma	Phase II	Dabrafenib plus trametinib	ICR: 44–59%	[49]
Melanoma	Phase II	Single arm: ipilimumab	ICR: 10–25%	[50]
Melanoma	Phase II	Single arm: pembrolizumab	ICR: 14%	[48]
Melanoma	Phase II	Nivolumab plus ipilimumab *versus* nivolumab alone	ICR: 42% *versus* 20%	[51]

BM, brain metastases; EGFR, epidermal growth factor receptor; HR, hazard ratio; ICR, intracranial response rate; NSCLC, non-small cell lung cancer; PFS, progression-free survival.

LUX 6 (8.2 *versus* 4.7 months; $p = 0.11$)].[59] The third-generation EGFR tyrosine kinase inhibitor osimertinib, in contrast to first- and second-generation EGFR tyrosine kinase inhibitors, also has activity in the presence of an *EGFR T790M* mutation, the most frequent point mutation causing therapy resistance to first- and second-generation EGFR tyrosine kinase inhibitors.[60] Osimertinib was recently shown to have a higher extracranial activity in patients with *EGFR*-mutated metastatic NSCLC than first-generation EGFR tyrosine kinase inhibitors.[45] Importantly, patients with asymptomatic BM could be enrolled and progression-free survival was statically significantly longer in BM patients treated with osimertinib compared with the ones treated with first-generation EGFR tyrosine kinase inhibitors [15.2 months *versus* 9.6 months; HR 0.47; 95% confidence interval (CI) 0.30–0.74; $p < 0.001$], offering an important new systemic treatment option in patients with asymptomatic *EGFR*-mutated NSCLC BM.[45]

ALK gene rearrangements are observed in about 5% and *ROS1* gene rearrangements in about 1–2% of nonsquamous NSCLC patients, again with a higher frequency in female patients as well as never-smokers, and serve as a predictive biomarker for response to ALK tyrosine kinase inhibitors.[61–64] The first-generation ALK tyrosine inhibitor presented with an intracranial disease control rate of 65% in asymptomatic BM patients; however, intracranial progression was observed in the majority of patients, suggesting that BM might be more likely to acquire resistance or that the intracranial efficacy is lower compared with the extracranial.[65] The second-generation ALK inhibitor ceritinib was shown to overcome resistance to first-generation ALK tyrosine kinase inhibitors, suggesting that sequencing might provide a new treatment approach.[66] However, no data on the efficacy of ceritinib in BM exist yet. The third-generation ALK inhibitors alectinib or lorlatinib presented with a much better intracranial efficacy and importantly, with a lower rate of intracranial failure compared with the previous generations of ALK inhibitors.[46,67–69] The third-regeneration ALK inhibitor lorlatinib was specifically design for high brain penetration. Consequently, 73% of patients harboring either *ALK* or *ROS1* rearrangements included in the phase I trial suffered from BM and an intracranial response rate of 46% [11/26 patients with measurable central nervous system

(CNS) disease] was observed in patients with previous ALK tyrosine kinase inhibitor treatment.[69] Recently, the intracranial efficacy of the third-generation ALK tyrosine kinase inhibitor was further supported by the finding of the ALEX and the ALUR trials.[46,70] Intracranial response rate of patients with asymptomatic BM at baseline was 54.2% in the alectinib group and 0% in the chemotherapy group, underscoring the value of this targeted therapy as a first-line treatment option in selected BM patients.[70] Further, intracranial progression-free survival in patients harboring BM at baseline was shown to be statically significantly longer with the alectinib *versus* crizotinib group (HR 0.40; 95% CI 0.25–0.54; $p < 0.001$), indicating a secondary preventive potential.[46]

Mutations of *BRAF* gene are predictive to response to combination of BRAF and mitogen-activated protein kinase kinase (MEK) inhibitors and occur in about 0.3% NSCLC patients.[71] So far, only a case reported suggested also intracranial activity of the a BRAF tyrosine inhibitor in *BRAF*-mutated NSCLC BM; however, given the good intracranial response rate to tyrosine kinase inhibitors in melanoma BM (reviewed below), this approach might be a feasible treatment option in patients with *BRAF*-mutated NSCLC BM.[72]

Immune-checkpoint inhibitors targeting the programmed cell-death 1 (PD-1) axis, including pembrolizumab, nivolumab or atezolizumab, have shown higher efficacy than standard chemotherapy in patients with PD-L1 expression > 50% in the first-line setting and irrespective of PD-L1 expression in further lines.[73–75] Importantly, a durable response in approximately 20% of patients can be observed, suggesting that long-term survival is possible. So far, only some smaller trials investigated the intracranial response rate in asymptomatic NSCLC BM patients and revealed a promising intracranial response rate of 33% without increase of any neurological side effects.[48] Further prospective trials are warranted to identify NSCLC BM patients profiting from immune-checkpoint monotherapy.

Systemic therapies in breast cancer brain metastases

Breast cancer is divided into several subtypes on the basis of gene-expression patterns, including the estrogen and progesterone receptor and the HER2 receptor, which are predictive of the response to endocrine and HER2-directed targeted therapies.[76] Overexpression of HER2 can be observed in approximately 10–15% of breast cancer patients and is associated with a frequent and early brain metastatic spread.[77] HER2-targeted tyrosine kinase inhibitors like lapatinib, as well as HER2-targeted antibodies like trastuzumab and pertuzumab, or HER2-targeted antibody drug conjugates like T-DM1, were shown to improve survival of patients with and without BM.[77–79] Importantly, patients of the HER2 breast cancer subtype have a particular favorable prognosis, even after diagnosis of BM, with a median survival of up to 24 months.[2] Therefore, therapies with late toxicities such as neurocognitive decline after WBRT have to be discussed with caution as a first-line treatment option.[2,80] The LANDSCAPE trial, as a proof of principle, showed that WBRT could be postponed by 8.3 months in patients with asymptomatic to oligosymptomatic BM by combined capecitabine and lapatinib treatment.[19] The intracranial response rate of 66% presented similar to the extracranial response rate (44.1%), suggesting that first-line systemic therapy should be evaluated as a treatment option in patients with multiple, oligo- to asymptomatic BM from HER2-positive breast cancer.[19,77,80] T-DM1 was also shown to have promising intracranial efficacy as a monotherapeutic approach in oligo- to asymptomatic patients, suggesting that the partly present blood–brain barrier breakdown is sufficient to allow a therapeutically effective concentration of this large antibody–drug conjugate.[79] Currently, the international phase II Kadcyla In pAtients With bRAin Metastasis (KIARA) trial is evaluating the therapeutic efficacy of T-DM1 monotherapy in patients' BM having HER2-positive breast cancer [ClinicalTrials.gov identifier: NCT03203616].

The luminal subtype, as defined by the presence of estrogen and progesterone receptor expression, is present in approximately 80% of all breast cancer patients and is sensitive to endocrine therapies.[80] There are no clinical data from prospective clinical trials on the value of endocrine monotherapy in breast cancer BM patients, and only some case reports and clinical case series argue that tamoxifen as well as megestrol acetate have intracranial efficacy.[81] Cyclin-dependent kinases (CDKs) 4 and 6 (CDK4/6) inhibitors are an important new target in luminal breast cancer as estrogen receptor signaling was shown to upregulate cyclin D1 levels and thereby potentiate multiple signaling pathways resulting in the upregulation of CDK4/6 activity.[82] Addition of a

CDK4/6 inhibitor (palbociclib, ribociclib, abemaciclib) to endocrine therapy in luminal metastatic breast cancer patients was proven to be superior compared with endocrine therapy alone in terms of progression-free survival.[83–85] So far, no efficacy data exist for patients with BM; however, ongoing clinical trials are currently evaluating this treatment option [ClinicalTrials.gov identifiers: NCT02774681, NCT02308020].

The triple-negative subtype, defined by the absence of estrogen and progesterone receptor, as well as HER2 overexpression, comprises about 10–15% of breast cancer cases and is associated with a particularly high incidence and early development of BM.[86] Unfortunately, no proven targeted therapies are currently available in this subtype; however, several promising agents, including immune-checkpoint inhibitors, are currently under investigation.[87]

Systemic therapies in melanoma brain metastases

Given the high propensity of metastatic melanoma patients to develop BM and the rather radioresistant properties of melanoma, targeted therapies are of particular importance in the treatment of melanoma BM.[88]

The mutation of *BRAF* gene with a substitution of valine to glutamate at codon 600 (*BRAF* V600E) is evident in about 50% of melanoma patients and is a predictive biomarker for the response to BRAF tyrosine kinase inhibitors like vemurafenib or dabrafenib. The combination of the BRAF inhibitor with an MEK inhibitor like trametinib and cobimetinib was shown to be more effective in terms of response and response duration compared with the BRAF inhibitor monotherapy in patients with metastatic *BRAF*-mutated melanoma.[89,90] The COMBI-MB phase II study investigated the intracranial response rate of the combination of dabrafenib plus trametinib in patients with: (a) *BRAF* V600E-positive, asymptomatic melanoma BM, with no previous local brain therapy; (b) *BRAF* V600E-positive, asymptomatic melanoma BM, with previous local brain therapy; (c) *BRAF* V600D/K/R-positive, asymptomatic melanoma BM, with or without previous local brain therapy; and (d) *BRAF* V600D/E/K/R-positive, symptomatic melanoma BM, with or without previous local brain therapy. Intracranial responses were 58% in group 1, 56% in group 2, 44% in group 3 and 59% in group 4, indicating that combined BRAF and MEK inhibition has a high intracranial efficacy also in patients with symptomatic BM and might therefore be a valid treatment option in selected patients.[49]

In patients with newly diagnosed metastatic melanoma, the standard treatment includes immune-checkpoint inhibitors that inhibit the PD-1 inhibitor (nivolumab, pembrolizumab) either alone or in combination with a cytotoxic T-lymphocyte protein 4 (CTLA4) inhibitor (e.g. ipilimumab).[91] Clinical efficacy of CTLA4 and PD-1 inhibitors as monotherapies in melanoma BM patients has been investigated in BM-specific trials. A phase II study on ipilimumab monotherapy in patients with melanoma BM included overall 72 patients in two cohorts. Cohort A (n = 51) included asymptomatic patients without corticosteroid treatment and cohort B (n = 21) patients with symptomatic BM requiring corticosteroid treatment.[50] Intra- (cohort A: 25%; cohort B: 10%) and extracranial (cohort A: 33%; cohort B: 10%) disease control rate was similar, although a numerical difference was observed between the asymptomatic patients (cohort A) and the symptomatic ones (cohort B), suggesting that corticosteroid treatment might indeed impact the efficacy of ipilimumab therapy due to the resulting immune suppression. Only very limited data from BM-specific trials on the intracranial efficacy of anti-PD-1 immune-checkpoint inhibitor monotherapy exist. A phase II trial on pembrolizumab monotherapy in BM patients included melanoma (n = 18) and NSCLC (n = 18) patients.[48] In this study, 4/14 (28%) melanoma patients (4 patients not eligible for response assessment) presented with confirmed intracranial partial response and 2/14 (14%) with stable intracranial disease, resulting in a 42% intracranial disease control rate. Conclusions have to be drawn with caution due to the limited number of included patients. Recently, two phase II trials investigated the combination of CTLA4 blockade (ipilimumab) with PD-1 blockade (nivolumab) in asymptomatic patients with no prior local BM therapy. Combination therapy was safe, as no increase in neurological side effects was observed in this particular patient population compared with patients without BM. The intracranial response rate was 42–55% (up to 21% experiencing a complete intracranial response) for patients treated with the combination compared with 20% in patients treated with the PD-1 inhibitor alone,

indicating that the combination of nivolumab and ipilimumab should be considered as first-line therapy for patients with asymptomatic untreated melanoma BM.[92,93]

Prevention of brain metastases by systemic therapies: the smarter approach?

Considering the limited therapeutic effect of local as well as systemic treatments in established, symptomatic BM, prevention of BM before they become clinically evident is an enthusiastically discussed clinical approach.[4,94,95] Accordingly, prophylactic cranial radiation has been repetitively investigated in patient cohorts with high risk of developing BM, like small cell lung cancer and NSCLC. However, considering the neurocognitive side effects and the absent or minor impact on OS, the indication for prophylactic cranial radiation is limited.[96]

Inhibition of pivotal steps of the brain metastatic cascade using targeted therapies with favorable toxicity profile in a population at high risk of developing BM could, therefore, be of high clinical impact: prevention of BM might be more effective and associated with less side effects compared with prophylactic cranial radiation.[97] As a proof of principle, NSCLC macrometastasis outgrowth, which is highly dependent on induction of neo-angiogenesis, could be prevented by the vascular endothelial growth factor (VEGF) antibody bevacizumab in a preclinical model.[98] The BM preventive potential of bevacizumab in NSCLC was further supported by the *post hoc* analysis of phase III trials investigating the combination of bevacizumab plus chemotherapy in patients with metastatic NSCLC. Here, BM as first site of recurrence was reduced significantly.[99] In contrast, no BM prevention was observed in breast cancer patients or in a preclinical melanoma BM model, as these entities present with less dependency on neo-angiogenesis induction during BM development.[98,99] Further, data from preclinical studies suggest that several frequently applied targeted therapy approaches with favorable side-effect profile might have preventive therapeutic potential. Here, the growth-reducing impact of an phosphoinositide 3-kinase (PI3K) inhibitor was shown to be greater on experiment, developing melanoma BM compared with the established macrometastases, suggesting that the therapeutic effect might be higher in a preventive compared with a therapeutic setting.[100] Accordingly, a preventive potential of the anti-alkylating chemotherapeutic compound temozolomide was suggested for experimental breast cancer BM, while the therapeutic effect in established BM was shown to be negligible.[101]

Only few clinical trials systematically investigated the BM preventive potential of targeted therapies. The CERBEL trial investigated the BM preventive potential of the HER2 tyrosine kinase inhibitor lapatinib, which in theory can pass the blood–brain barrier, *versus* the HER2 antibody trastuzumab, which cannot pass an intact blood–brain barrier due to the high molecular weight. However, the trial was terminated early owing to poor accrual, and no statistically significant difference in BM occurrence was observed.[102]

The occurrence of BM as first site of relapse was investigated as an exploratory secondary endpoint in several recent, large phase III trials (Table 2). The FLAURA trial investigating osimertinib *versus* standard EGFR tyrosine kinase inhibitor (erlotinib or gefitinib) showed that CNS progression was reduced in the osimertinib arm (6% *versus* 15%) suggesting a BM preventive potential for the third-generation EGFR tyrosine kinase inhibitor.[45] Similarly, a BM preventive potential was argued for third-generation ALK tyrosine kinase inhibitor alectinib (compared with first-generation ALK tyrosine kinase inhibitor crizotinib) in the ALEX trial, as BM at first site of relapse was reduced (4.6% *versus* 31.5%).[46] Importantly, a secondary preventive potential for prevention of BM relapse after initial local therapy approach was also suggested for erlotinib compared with gefitinib (30 *versus* 15.8 months; $p = 0.024$), as well as for alectinib compared with crizotinib (HR 0.18; $p < 0.0001$), further underscoring the importance of investigating BM-specific endpoints in clinical trials.[46,47,103]

Interestingly, a preventive potential was also investigated for immune-checkpoint inhibitors, which, in contrast with targeted therapies, have no direct effect on the tumor cells but reveal their therapeutic potential *via* the induction of an antitumor immune response. Authors of the PACIFIC trial are investigating the efficacy of durvalumab addition to radio/chemotherapy in a cohort of stage III NSCLC patients who are treated with potential curative attempt, making BM prevention even more crucial.[104] BM as first site of relapse was statistically significantly less frequently observed in the durvalumab group

Table 2. Selected trials investigating BM-specific prevention by targeted therapies.

Entity	Phase	Study design	BM progression rate	Reference
EGFR-mutated NSCLC (stage IV)	Phase III	Osimertinib *versus* first-generation EGFR tyrosine kinase inhibitor	6% *versus* 15%	45
ALK-mutated NSCLC (stage IIIb, IV)	Phase III	Alectinib *versus* crizotinib	4.6% *versus* 31.5% (HR 0.14; $p < 0.0001$)	46, 47
NSCLC (stage III)	Phase III:	Combined radio/chemotherapy with or without durvalumab	5.5% *versus* 11.0%	104

BM, brain metastases; EGFR, epidermal growth factor receptor; HR, hazard ratio; NSCLC, non-small cell lung cancer.

compared with the control group (5.5% *versus* 11.0%), underscoring this combination as a promising therapeutic, as well as a preventive approach in stage III NSCLC patients.[104,105]

Ideally, prospective clinical trials should validate these BM preventive results and help to define patient groups eligible for BM-preventive therapeutic strategies.

Conclusion

BM patients still represent a population of high clinical need, as new developments in therapeutic approaches were long limited due to the systematic exclusion of BM patients from clinical trials.[4] However, recent phase III trials, as well as some BM-specific phase II trials, have addressed specific BM outcome parameters that could prove a promising activity of systemic therapies in patients harboring BM. Therefore, systemic therapies have become an important treatment backbone in patients with oligo- to asymptomatic disease, in order to prevent neurological side effects in this population, with favorable survival prognosis.[2,106] Redefining indications of WBRT and SRS, as well as new application methods like hippocampal-sparing WBRT, further help to reduce treatment-induced neurological deterioration. Future studies have to further investigate the possibility of postponing WBRT in selected patients by application of first-line systemic treatment.

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