ESMO Open Cancer Horizons

Recent advances in the biology and treatment of brain metastases of non-small cell lung cancer: summary of a multidisciplinary roundtable discussion

Matthias Preusser,[1] Frank Winkler,[2,3] Manuel Valiente,[4] Christian Manegold,[5] Elizabeth Moyal,[6] Georg Widhalm,[7,8,9] Jörg-Christian Tonn,[10] Christoph Zielinski[1]

To cite: Preusser M, Winkler F, Valiente M, *et al*. Recent advances in the biology and treatment of brain metastases of non-small cell lung cancer: summary of a multidisciplinary roundtable discussion. *ESMO Open* 2018;**3**:e000262. doi:10.1136/esmoopen-2017-000262

Received 18 August 2017
Revised 21 November 2017
Accepted 29 November 2017

For numbered affiliations see end of article.

Correspondence to
Professor Matthias Preusser; matthias.preusser@meduniwien.ac.at

ABSTRACT

This article is the result of a round table discussion held at the European Lung Cancer Conference (ELCC) in Geneva in May 2017. Its purpose is to explore and discuss the advances in the knowledge about the biology and treatment of brain metastases originating from *non*-small cell lung cancer. The authors propose a series of recommendations for research and treatment within the discussed context.

INTRODUCTION

Recent insights into the biology of *non*-small cell lung cancer (NSCLC) have led to a wealth of novel therapies, including targeted agents and immune checkpoint inhibitors with significant clinical activity. So far, there are limited data on the efficacy of these drugs in patients with brain metastases (BMs) but intracranial responses have been documented in emerging studies.

At the meeting, a multidisciplinary group of experts discussed the biology of BMs as well as the anatomy of the blood–brain barrier (BBB). The group considered treatment options for NSCLC and their effect on BMs, focusing on targeted treatment and combination treatment for epidermal growth factor receptor (EGFR) mutated NSCLC and those with anaplastic lymphoma kinase (ALK) rearrangement.

Incidence of BMs in NSCLC

BMs are the most common intracranial neoplasms with significant morbidity and mortality.[1 2] In lung cancer, 30–50% of patients will be diagnosed with BMs during their disease, with rising frequency because of the availability of novel imaging techniques and improved survival rates. Fifty per cent of lung cancer BMs occur at disease presentation and 50–60% as the only site of distant disease. BMs often present as multiple lesions, although in one third of patients BMs are singular.

BMs occur initially in 20% of patients with NSCLC,[1] in 10–20% with advanced NSCLC,[3] with numbers as high as 40–50% in those with stage III lung adenocarcinoma,[4] 20–40% in those with ALK-rearranged tumours,[5] and 45–70% in those who have ALK-rearranged NSCLCs and have been pretreated with an appropriate tyrosine kinase inhibitor (TKI).[3]

EGFR-activating mutations are present in about 10–20% of white patients with NSCLC.[6 7] In patients with EGFR mutation, the incidence of BMs at the time of diagnosis is 25%, which is slightly higher than in unselected patients, suggesting that EGFR mutations might be associated with a metastatic tropism to the brain and then with an increased risk of BMs.[8 9] Furthermore, the brain is a common site for relapse of disease in patients previously treated with TKIs in about 30–60% of EGFR-mutated NSCLCs.[10]

Prognosis of BMs

Overall survival (OS) of patients after the diagnosis of BMs remains poor with significant clinical problems. The prognosis depends on the patient's age and performance status, the type of the primary tumour, the time from diagnosis of the primary, the overall disease activity, and the location and extension of extracranial and intracranial disease.[11–14]

Biology and molecular alterations of NSCLC BMs

There are many biological aspects of growth of metastases in the brain for which scientific progress has been made and where further progress in our understanding will be helpful in developing new treatments. This extends from the biology of brain colonisation by metastatic cells from the initial stages (asymptomatic metastases) to advanced stages when the disease is clinically diagnosed.

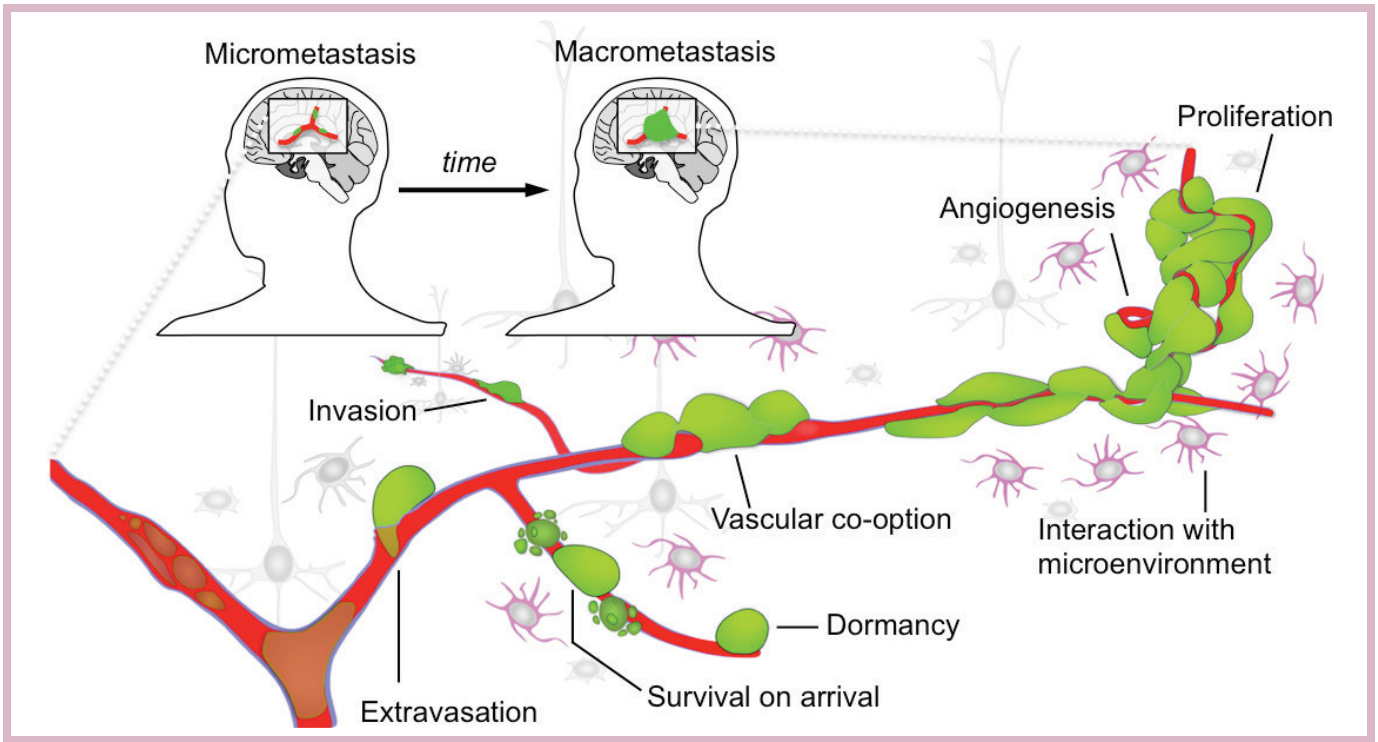

Figure 1 Key mechanisms of a metastatic cell developing in the brain (see reference[22]).

The use of experimental models has allowed construction of a sequential map showing key mechanisms of a metastatic cell developing in the brain (see figure 1).

Crossing the BBB

The ability of cancer cells to cross the BBB involves general and specific mediators.[15–18]

The naive brain microenvironment

After extravasation most metastatic cells die, partly due to reactions of the brain microenvironment responding to their presence.[19–21] This suggests that a naive brain microenvironment initially repels many potential cancer cells. Some molecular mediators of natural defences have been reported.[20 21] It is also true, unfortunately, that some metastatic cancer cells avoid this initial bottleneck by blocking anti-tumour components of the reactive microenvironment.[20 21] The surviving cells closely interact with pre-existing blood vessels in the brain by vascular co-option and colonisation of the crucial perivascular niche.[19 21 22] This is all mandatory to the final progression to brain macrometastases.

Vascular co-option and dormancy

This process is mediated by cancer cell adhesion molecules and integrins,[21 23] as well as by secreted molecules from the co-opted endothelial cells.[24 25] Brain metastasis can manifest many years after the diagnosis of the primary tumour. Dormancy/quiescence is thought to play an important role in brain metastasis and recent data have started to show mediators of this biology,[26] which is also linked to the perivascular location. Eventually these cells will re-awake and start to grow aggressively. The mechanism mediating this process has been linked to the ability of cancer cells to recognise components of the basal lamina.[23 27]

Angiogenesis

Additional ways to interact with the vasculature involve the formation of new blood vessels, called angiogenesis. This appears crucial for the formation of BMs from lung adenocarcinoma, in an entity-specific and organ-specific manner. Interestingly, inhibition of this early angiogenic switch prevented metastases from outgrowth and arrested them in a microscopic state, making angiogenesis inhibition an interesting approach for BM prevention in lung adenocarcinoma.[19 28]

Invasive fronts

Even though the mechanisms of brain colonisation are more linked to the initial stages of metastasis, some might also apply to advanced stages of the disease and thus offer opportunities for improved therapies. For instance, invasive fronts have been described in 50% of BMs, which in many cases correlates with the process of vascular co-option.[29] The correlation of invasive fronts with poor prognosis in patients with BMs[30] might offer a therapeutic window to target mediators of vascular co-option after surgery to reduce local relapse.

Genomic alterations

Therapies, including targeted ones that are effective outside the brain, can fail in this organ; reasons for this might include the genomic and other molecular divergence of BMs compared with primary tumours and other metastatic sites.[31–37] Although still in need of

more evidence for their contribution to BM progression, specific genomic alterations found in brain metastasis offer actionable mutations to be exploited. In addition, BM-specific mutations could also be found in liquid biopsies from blood or cerebrospinal fluid (CSF) and have been used to evaluate response to therapy and the presence of residual disease.[33 36] This emerging field of BM would benefit from the use of recent advances in genetic engineering using CRISPR/Cas9 combined with experimental models.

Cancer cell–brain microenvironment interaction as target for therapy and prevention

The divergent evolution of metastatic cells in the brain might respond to the significant pressure generated by its environment that is made of different cellular components, and homeostatic regulation. The microenvironment thus might be a crucial pillar to explain the specificity that applies to brain metastasis. Close cancer cell–microenvironment interactions have created an interesting scenario, where experimental therapies have probed the critical support that cancer cells receive from altered components of the microenvironment. For instance, established BMs have been shown to assemble gap junctions with surrounding reactive astrocytes.[38–42] This interaction can allow metastatic cells to detoxify themselves from the accumulation of potentially toxic metabolites generated by various sources of stress, including chemotherapy.[42] A combination of BBB-permeable drugs targeting gap junctions has recently supported the potential of targeting interactions with the microenvironment. This might offer BM-specific therapies and prevention strategies in the future, possibly independent of the tumour entity.

THE RELEVANCE OF THE BBB FOR MEDICAL TREATMENT OF NSCLC BMS

The BBB is the physical, chemical and metabolic barrier that segregates blood from the interstitial fluid of the central nervous system (CNS) for protection of the CNS against overexposure, pathogens and toxins. Molecules with a molecular weight over 500 Daltons (the molecular weight of 98% of drugs) are generally considered to not readily cross an intact BBB, but other physico-chemical properties also influence brain penetration. This is important for primary and secondary prophylaxis; however, mixed responses have been seen.

The rising incidence of BMs may be partly due to the fact that some therapeutic compounds can control tumour growth outside of the CNS but do not, or only partially, penetrate the BBB.[43] Therefore, tumour cells that have successfully invaded the brain may not be affected by these agents, making the brain a potential 'sanctuary site' for cancers.[44]

There is an ongoing controversy about the role of the BBB breakdown in affecting the activity of systemic therapies for BMs.[45 46] In health, but also many CNS diseases, the specific anatomical and molecular constitution of the BBB limits access of the vast majority of molecules to the brain: specialised endothelial cells connected by tight junctions, the vascular basement membrane, pericytes, astrocytic foot processes, and specialised transporter systems strictly regulate extravasation, while active exclusion mechanisms like glycoprotein P (P-gp), breast cancer resistance protein (BCRP) and the family of multidrug-resistant proteins exclude xenobiotics effectively.[47] Thus, the BBB remains a complex obstacle for drug delivery to the CNS. Several techniques have been tested to direct therapeutics across the BBB, including disruption of the BBB, modification of drugs, inhibition of efflux transport, and Trojan horse approaches that use endogenous transporter properties of the BBB.[48] One problem with those approaches is that even if an active compound can cross the endothelium, it is not guaranteed that it will reach the target cell. Recent evidence suggests that lowering the affinity of an antibody directed against the transferrin receptor allows for greater release of the antibody on the abluminal surface of the vessel, and entry into the brain parenchyma.[47 49]

The majority of brain macrometastases, that is, metastases of more than 1 mm diameter which are detectable with common imaging techniques, do show signs of disturbance of the BBB, although to a varying extent.[50–53] Therefore, the challenges of crossing the normal BBB do not fully apply to BMs, even though some aspects of the BBB are preserved in BMs. It is a matter of debate whether a BBB breakdown in brain tumours allows penetration of systemic chemotherapies to the single cancer cells of the brain tumour in sufficient concentrations. In clinical specimens, highly variable tumour levels have been reported for different agents.[54 55] Of note, lapatinib and trastuzumab, two agents with no significant activity against breast cancer BMs, can be found in relevant concentrations in BMs in clinical and preclinical specimens, which makes it highly likely that the BBB is only partially relevant for the lack of CNS activity of some drugs.[55 56] In accordance with this, it has been demonstrated that trastuzumab-emtansin (T-DM1), a derivate of trastuzumab, is able to show signs of clinical effectivity in HER2-overexpressing BMs, further supporting the notion that it is not the BBB penetration but other microenvironmental mechanisms in the brain that make certain drugs ineffective.[57]

It has been shown that increased BBB permeability is associated with accelerated metastasis growth.[58] Two closely related mTOR/PI3K inhibitors, one of them with a minor chemical modification that allows the two main exclusion transporters constituting the BBB (P-gp and BCRP)[59] to be bypassed, had different effects on these metastases: while the BBB non-permeable inhibitor only affected permeable metastases, the BBB permeable one had strong anti-tumour effects on non-permeable micrometastases, and even dormant cancer cells in the brain.[58] Furthermore, nuclear morphology changes and single cell regression patterns implied that both

inhibitors target cancer cells independently of their relative position to the blood vessel, making BBB permeability the limiting step for drug diffusion to cancer cells in the brain.[58] Another preclinical study found a highly variable uptake of doxorubicin and paclitaxel of different metastases from the same breast cancer cell line, so that cytotoxic concentrations were reached in only 10% of the most permeable metastases.[52] It is widely assumed that classical chemotherapies with proven activity on systemic metastases of many cancers have limited, if any, activity on BMs,[60] probably with the exception of primary chemotherapy of lung cancer BM.[61] This can be due to a lack of sufficient BBB breakdown to allow primary extravasation of the drug and rapid secondary exclusion by P-gp, but also specific resistance mechanisms that are different in the brain, such as protection of extravasated cancer cells by astrocytes[38] or other brain resident cells.

TREATMENT OF NSCLC BMS

Overview

For a long time, BMs in lung cancer have been considered a final event and were treated either by whole brain radiation therapy (WBRT) or palliative care. However, since the arrival of new systemic and targeted therapies, more effective treatments for BMs are available with the aim to increase local control, and if possible survival, without affecting neurocognition.

Current treatment algorithms of NSCLC BMs offer symptom control measures and therapeutic measures. Modern disease-directed management includes:[62]

- surgical resection,
- radiotherapy,
- chemotherapy,
- targeted drugs,
- multi-modality approaches.

Limited metastatic lesions

For limited metastatic lesions (one to three metastases) neurosurgical resection is one of the main therapeutic options, with stereotactic radiosurgery (SRS) being the main alternative, known to be equivalent to surgery in term of local control.

Resection can also be combined with radiotherapy, such as SRS or WBRT. These combinations have been addressed in two recent randomised trials, which showed that postoperative SRS was associated with a significant increase in local control compared with observation[63] and that postoperative WBRT was associated with an increase in neurocognitive deterioration compared with postoperative SRS without any difference in OS.[64]

Another approach is the combination of SRS and WBRT. One recent randomised trial has shown that even if WBRT combined with SRS is associated with better brain control, WBRT induces significant higher neurocognitive deterioration compared with SRS alone, without any difference in OS.[65] However, another randomised trial comparing WBRT plus SRS with SRS alone showed that for a subgroup of patients with good graded prognostic assessment, a benefit of adding WBRT to SRS was obtained in OS.[66]

While treating patients with WBRT, neurocognition can be preserved by performing hippocampal sparing[67] or adding mementine.[68] A randomised phase III clinical trial aiming to compare time to neurocognitive failure between WBRT plus mementine to WBRT with hippocampal preservation and mementine is currently being performed (ClinicalTrials.gov identifier: NCT02360215).

Multiple metastatic lesions

In multiple metastatic lesions (more than three BMs) WBRT is still an option for most patients, alone or in combination with SRS, a radio-sensitiser or chemotherapy. However, SRS on more than four and up to 10 BMs is feasible,[69] with no more late toxicity in neurocognition compared with patients with one to four brain metastases.[70] Some patients, especially those with a poor performance status, receive chemotherapy or steroids alone.[71] The addition of targeted drugs such as erlotinib as radio-sensitisers to WBRT has failed to show benefit in local controls or OS but has increased toxicity.[72–77] The addition of chemotherapeutic agents such as temozolomide to radiation has also failed to improve survival but increases toxicity.[78–82]

Systemic chemotherapy

Chemotherapy plays a limited role in the treatment of BMs because of its inability to cross the BBB. However, response rates as high as 30–40% have been reported in the brain with platinum-based chemotherapy, similar to rates observed extracranially.[61 83]

Targeted drugs

EGFR TKI therapy

Among patients with NSCLC with EGFR mutations, TKIs seem more effective than chemotherapy in controlling intracranial disease. EGFR TKIs are low molecular weight organic compounds with low to moderate CSF penetration rates differing between first-generation to third-generation drugs.[84 85]

EGFR TKIs of the first generation, such as gefitinib and erlotinib, and of the second generation, such as afatinib, have recently been integrated in the treatment algorithm of advanced metastatic mutated NSCLC as first-line therapy, replacing conventional chemotherapy because of improved response and survival rates.[86–88]

Retrospective data and phase II study experiences have indicated that gefitinib and erlotinib have significant intracranial activity.[89 90]

For afatinib, phase II data, results from a compassionate use programme as well as pre-specified subgroup analyses suggest significant intracranial efficacy. This substantiates preclinical and clinical observations that afatinib can penetrate the BBB at concentrations sufficient for initiating anti-tumour activity.[91–93]

EGFR TKIs of the third generation, such as AZD 3759 and osimertinib, have recently accelerated the debate over the role of modern targeted therapy for the treatment of BMs in mutated NSCLC as a potential substitute for brain radiation. This is because of preclinical and clinical evidence proving them to be more effective, showing a promising blood brain penetration and the potential to overcome EGFR TKI resistance. They also challenge the concept of upfront WBRT by being potentially more effective but less neurotoxic.[94–97]

Preclinical studies have shown that osimertinib induces sustained tumour regression in an EGFR-mutated PC9 mouse brain metastasis model,[36] and exhibits a greater distribution into mouse brain tissue than gefitinib, rociletinib or afatinib. Clinically, osimertinib has greater efficacy than platinum/pemetrexed in patients with T790M-positive NSCLC, including those with CNS metastases in a second-line setting.[86 95]

AZD 3759 has primarily been designed for crossing the BBB. Clinical experience for AZD 3759 exists from a phase I study in pretreated patients. By dosing up to 300 mg twice a day, there has been a significantly higher tumour shrinkage intracranially than extracranially. Grade 4 toxicity of less than 10% was reported for rash, diarrhoea and pruritus.[96 97]

TKIs for patients with ALK-rearranged NSCLC

Currently, there are five compounds registered for patients with NSCLC and ALK rearrangement: these are the TKIs crizotinib, ceritinib, alectinib, lorlatinib and brigatinib. All these compounds have been registered with the US Food and Drug Administration (FDA); crizotinib, certinib and alectinib have also been approved by the European Medicines Agency (EMA) with an approval of brigatinib currently pending.

The development of the ALK-directed TKI crizotinib took a rather short time between the discovery of the importance of ALK rearrangement and the introduction of the drug. In the PROFILE 1014 trial, crizotinib showed a significant improvement in progression-free survival (PFS) compared with chemotherapy in patients with ALK rearrangement.[98]

The incidence of BMs constitutes a major problem in patients with NSCLC and ALK rearrangement. About one third of TKI-resistant tumours harbour ALK mutations, including an amplification which occurs in 10% of mutations of the remaining 25%.[99–103]

Therefore, the question arises whether the CNS acts as a ‘sanctuary’ for the development of metastases, as up to 70% of recurrences occur within this anatomic area.

Drugs developed after crizotinib, targeting ALK rearrangement, such as ceritinib, alectinib and brigatinib, have the ability to induce a remarkable CNS response in patients who have been pretreated with crizotinib. They have quite a different side-effect profile however.

When considering alectinib, responses in the CNS were complete in 20% in patients with measurable CNS metastases,[104] whereas the use of brigatinib in the identical setting produced intracranial overall response rates in 42%–67% of patients.[105]

Very recent data have shown a significant superiority of alectinib over crizotinib in untreated ALK-positive NSCLC regarding the duration of PFS and the time until CNS progression.[106]

Nevertheless, the question of the best treatment sequence – if any - emerges and will have to be the topic of further clinical investigations.

Radiotherapy

Apart from surgery and targeted drugs, radiotherapy (especially radiosurgery or hypo-fractionated stereotactic radiotherapy (HFSRT)) is one of the main weapons to increase local control, and if possible survival, without affecting neurocognition.

Because the combination of WBRT with SRS or surgery does not increase OS but neurocognitive deficit[65 107 108] and because SRS alone compared with the combination of SRS with WBRT has been shown to lead to the same OS and less neurocognitive deficit, with a shorter time to intracranial failure, SRS is now considered a standard treatment for patients with BMs.

A study from 2016 showed the relevance of postoperative SRS compared with observation, bringing better local control without toxicity and no difference in OS.[109] More recently this has been confirmed by a randomised clinical trial showing that postoperative SRS led to significantly higher local control than observation, with the same OS.[63] The trial showed a higher benefit of postoperative SRS for small cavities (0–2.5 cm) compared with large ones.

Another randomised trial comparing postoperative radiation with WBRT plus SRS on non-resected BMs versus SRS on the cavity of resected metastases plus SRS on non-resected BMs showed that postoperative WBRT led to a higher neurocognitive deficit and the same OS compared with SRS alone. However, this trial showed poorer local control and worse brain control for patients treated with postoperative SRS compared with those treated with WBRT.[64]These conflicting results could be due, at least in part, to the presence of microscopic tumour infiltration not targeted by postoperative SRS. If local control is important, we have to address and aim to obtain better brain control without neurocognitive deficit, as well as a better OS. This is when the combination of radiotherapy, especially SRS or HFSRT, with targeted drugs or immunotherapy comes in to optimise BM treatment.

Combination and sequencing of medical therapies with radiotherapy for NSCLC BMs

The irradiation anti-tumour effect is driven by direct and indirect effects. Irradiation can induce tumour cell death as mitotic cell death, apoptosis, but also autophagy and senescence.[110]

SRS or HFSRT acts through the induction of apoptosis of endothelial cells, thus leading to tumour radio-sensitisation.[111] More recently it has been shown that irradiation can induce an immune cell death through CD8 T-cell infiltration and by the stimulation of tumour antigen presentation.[112 113] It has been shown that SRS could induce the expression of programmed death ligand 1 (PDL1) in tumours and that association of SRS and programmed cell death protein 1 (PD1) treatment led to radio-sensitisation in preclinical models.[114]

In addition to the local effect of radiotherapy in combination with immunotherapy, radiotherapy is also able to induce an abscopal effect, that is, an anti-tumour effect outside the irradiation field. This could be of great interest in tumours with high metastasis potential, such as lung cancer.

Radiotherapy and TKIs

To optimise the effect of SRS or HFSRT in NSCLC BMs, the combination of targeted drugs with such irradiation is a promising treatment. EGFR-mutated as well as ALK-positive NSCLCs have a higher risk of BMs, and EGFR as well as ALK pathways are known to control radio resistance. The association of EGFR inhibitors or ALK inhibitors with radiotherapy will lead to radio-sensitisation. Even if such inhibitors already penetrate the BBB, radiotherapy is known to disrupt the BBB and will help these inhibitors to penetrate. Several studies have shown the relevance of the combination of SRS or WBRT with TKIs with regards to intracranial progression but also, for some of them, in terms of OS. A pooled analysis showed that the combination of radiotherapy and TKIs had significant benefits in terms of objective response rate, time to intra-cranial progression and OS.[115] A recent retrospective study showed that WBRT and TKI treatment led to longer time to intracranial progression compared with SRS and TKI, or TKI alone.[116] Another retrospective study showed that patients with exon 21 mutation, when treated with WBRT and TKI, had a significantly higher OS and PFS compared with those treated with TKI alone.[117] No difference was seen for patients with exon 19 deletions. Also, a recent study showed that performing radiotherapy (SRS or WBRT) before TKI treatment significantly increased the median OS compared with radiotherapy only in the case of failure,[118] suggesting that SRS before EGFR TKI treatment is better than TKIs alone, at least for patients with exon 21 mutations. However, randomised trials need to be performed in this area.

A few trials are currently being undertaken associating SRS with ALK inhibitors and these should be developed.

Radiotherapy and immunotherapy

Another possibility is the combination of immunotherapy and radiotherapy, particularly SRS with checkpoint inhibitors. These combinations have been mostly studied in melanoma BMs, with SRS and ipilimumab treatment, but anti-PD1 and SRS combinations have also been reported.[119 120] Some studies report encouraging results even for OS, while others do not.[121] Some recent retrospective studies have shown that SRS performed before and concurrently to immunotherapy would have better results than SRS performed after.[120 122 123] Because of the incidence of pseudo-progression with these combined treatments, the evaluation of their efficacy needs to be performed with multimodal imaging (see figure 2). Again, clinical trials for the evaluation of such combinations in NSCLC BMs in patients without mutation, but also in those with EGFR mutation, are needed.

Neurosurgical resection of NSCLC BMs

Neurosurgical resection of BMs in patients with NSCLC is an indispensable treatment option in the multimodal management of such tumours. The subsequent initiation of postoperative radiotherapy in these tumours has demonstrated a positive impact on OS.[124 125] Furthermore, the extent of resection in NSCLC BMs is an important factor for patient prognosis. Thus, a complete 'macroscopic' removal of surgically treated BMs results in a significantly better patient prognosis than an incomplete tumour resection.[126] However, local recurrence of BMs after neurosurgical resection is not uncommon in clinical practice even after macroscopic complete resection and postoperative radiotherapy.

It was long assumed that BMs are well demarcated from the surrounding brain tissue. In 2013 Berghoff *et al* found in an autopsy study that only about half of the BMs show a well demarcated growth pattern. Tumour infiltration of the surrounding brain tissue of metastases was observed in the other half of cases. Perivascular growth into the brain parenchyma distant from the brain metastasis ('vascular co-option') was present in 18% of cases and diffuse infiltration of the surrounding brain tissue ('diffuse infiltration', like in a malignant glioma) was observed in 32% of cases.[29]

In a recent prospective study, Siam *et al* found that tumour infiltration of the surrounding brain tissue is a common finding especially in BMs from NSCLC, present in 75% of cases. In some of these NSCLC BMs the tumour infiltration was observed more than 2 mm away from the resection cavity.[30] Thus, tumour cells might remain in the surrounding brain tissue despite a complete 'macroscopic' resection of BMs and result in local recurrence.

To overcome this limitation, Yoo *et al* proposed a 'microscopic total resection' of single BMs in non-eloquent areas with additional removal of at least 5 mm of surrounding brain tissue. Such a microscopic total resection resulted in a significantly better local tumour control rate in BMs than conventional complete resections. However, this 5 mm safety margin in microscopic total resections was arbitrarily selected[126] and thus a more selective tool to visualise tumour infiltration of the surrounding brain tissue of BMs would be of interest.

5-Aminolevulinic acid

One innovative approach might be the selective visualisation of brain metastasis tissue with the intraoperative fluorescence marker 5-aminolevulinic acid (5-ALA). In a

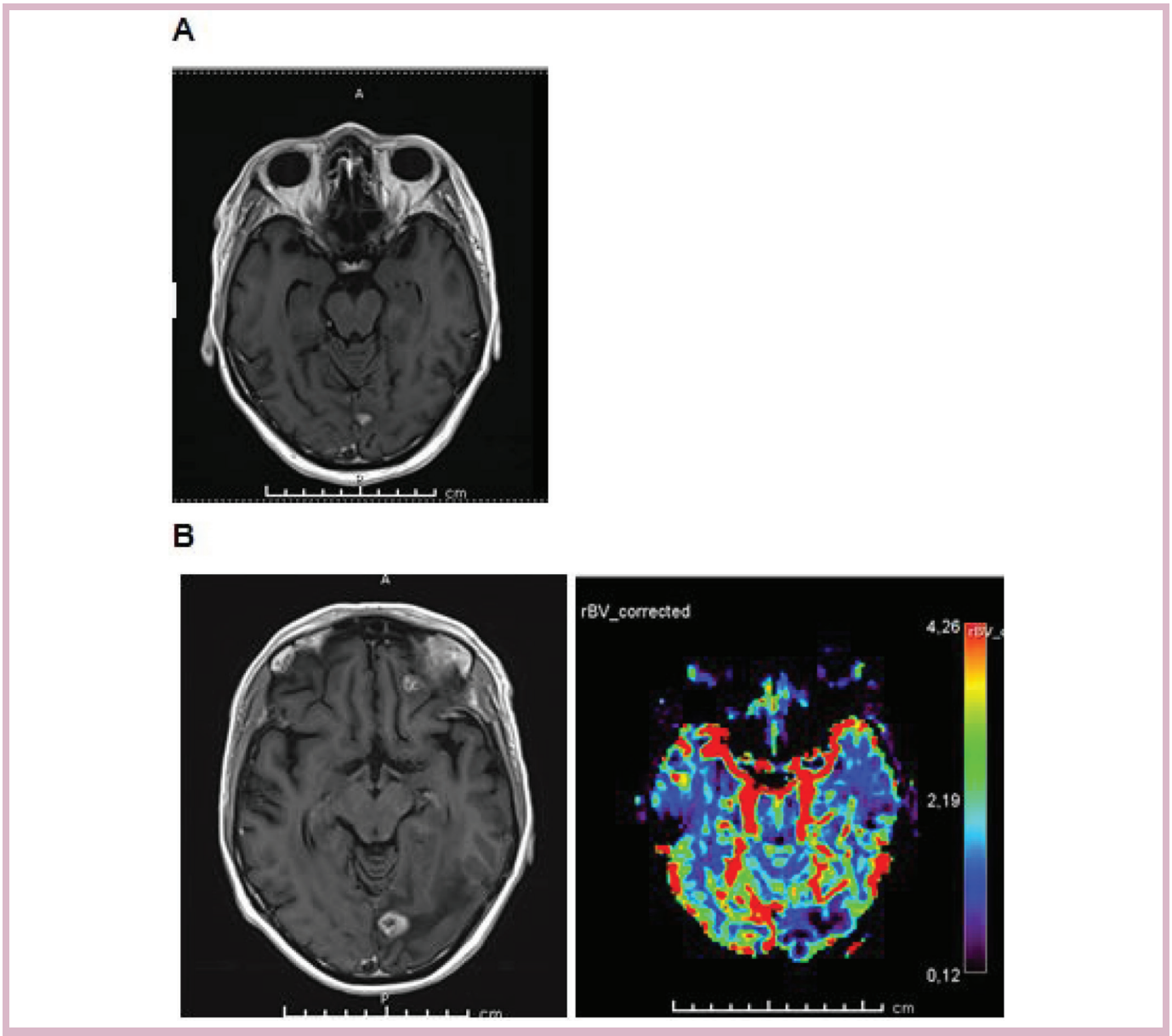

Figure 2 Pseudo-progression after sterotactic radiosurgery (SRS) and anti-programmed cell death protein 1 (PD1) treatment for a lung brain metastasis. Before SRS treatment (A) and 6 months after SRS and anti-PD1 treatment (B); increase in the irradiated brain metastasis on T1 gadolinium MRI, without vascularisation on perfusion.

recent study, Kamp *et al* found that BMs can be visualised during surgery with the assistance of 5-ALA in about two thirds of cases[127] (see figure 3). It is not clear so far if the 5-ALA fluorescence technique is also able to visualise tumour infiltration of the surrounding tissue of BMs. This should be investigated in multi-centre studies.

Neurosurgical interventions for the analysis of drug concentrations and biomarkers

Concept of 'window of opportunity' studies: measurement of tissue concentrations of antineoplastic agents in BMs

BMs have been widely considered 'extra-axial' lesions, thus not being restricted by the BBB. In contrast to gliomas, penetration of antineoplastic drugs from the intravascular space into the tumour tissue of BMs is less a matter of debate.[62] However, solid data are scarce. Mostly, there has been indirect evidence for drug tissue penetration into BMs due to observation of any response in MRI scans after systemic chemotherapy.[58 128] Recently, scores derived from blood values have been described to estimate survival of patients with BMs.[129] Only a few studies are available dealing with the measurement of tissue concentrations of antineoplastic agents in BMs. In a m eta-analysis of 1441 potentially relevant publications, only 12 turned out to provide solid data on tissue concentrations of chemotherapeutic drugs in BMs.[54] The tissue-to-blood ratio showed huge variations between different drugs which had also been used for solid tumours with subsequent BMs. As microsurgical resection offers direct access to the tissue, exposure of the patient to systemic therapy prior to surgery would allow the tissue

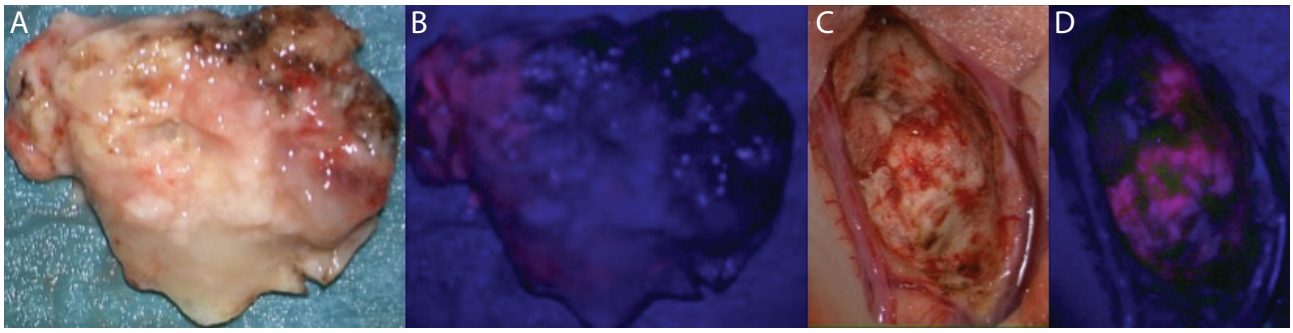

Figure 3 Application of 5-aminolevulinic acid (5-ALA) induced fluorescence during resection of a brain metastasis. Parts of the brain metastasis specimen derived from resection (A) can be visualised by 5-ALA-induced fluorescence (B). After surgical resection of the brain metastasis (C), the surrounding, potentially still tumour-infiltrated, brain tissue demonstrates 5-ALA-induced fluorescence (D).

concentration within the specimen to be quantified. Since the intravascular space contributes hereto, pharmacodynamics and pharmacokinetics of the compound must be considered to correct the values measured accordingly. Prerequisites of such a study would be:

- the drug should be in use for cancer therapy,
- phase I studies are already completed,
- the toxicity is known and reasonably low,
- there are no side effects which could be relevant for surgery (significant immediate or early bone marrow toxicity, embolic or bleeding disorders),
- the serum half-life (tissue half-life) is known to find the most appropriate timing of drug delivery in relation to tissue sampling,
- there is a calculation of serum level to estimate the influence of the intravasal drug,
- intra-operative pharmacokinetics if applicable.

Morikawa *et al* conducted such a study for capecitabine and lapatinib in BMs of breast cancer.[55] Capecitabine and lapatinib were shown to penetrate to a significant but variable degree into BMs of breast cancer. However, drug delivery to the BM tissue was variable and appeared in some cases too low to be effective. Overall, the tissue concentration varied considerably between the few cases under investigation, especially according to different preoperative dosages and timing of drug administration in relation to the surgical procedure. This highlights the importance of standardising such protocols to generate meaningful data. Thus, it could be crucial to elucidate mechanisms which limit drug concentration.

Such window-of-opportunity studies could be a promising tool to obtain information about inter-individual

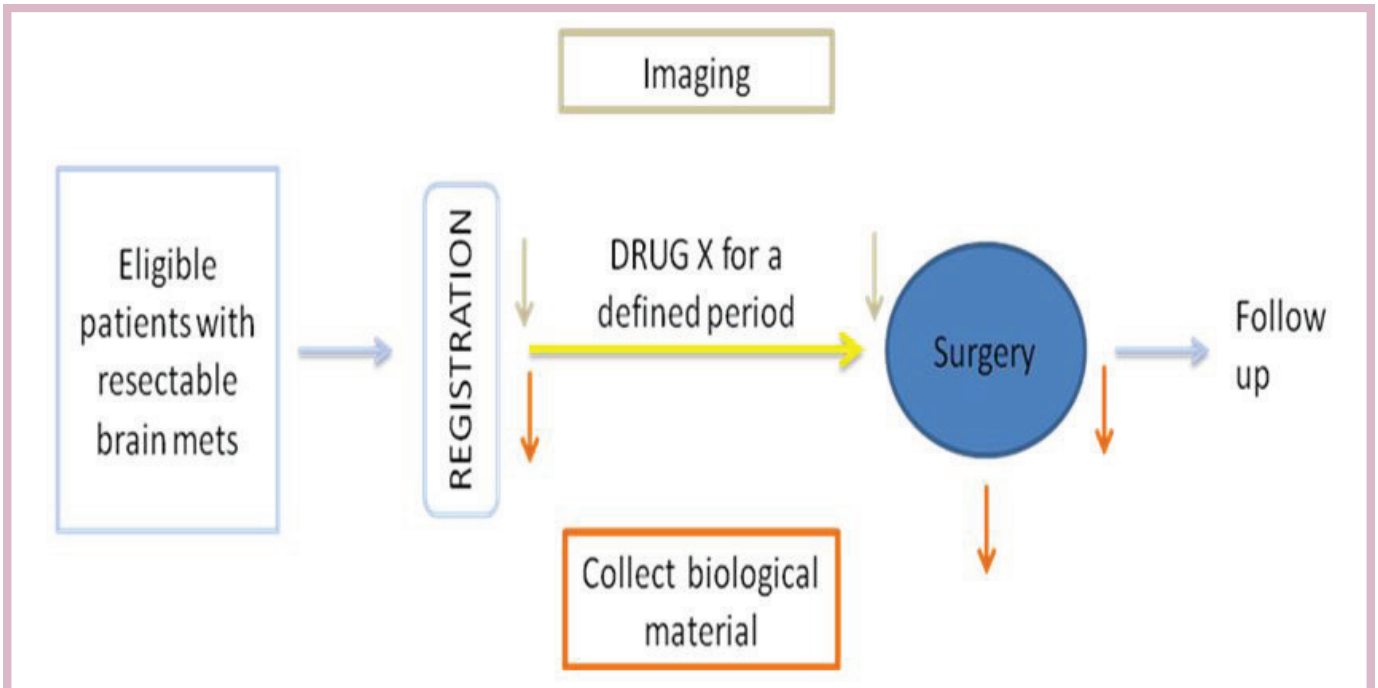

Figure 4 Concept of a window-of-opportunity study to obtain information about inter-individual variation of drug concentrations and optimal drug dosage of new compounds for systemic treatment of brain metastases.

variation of drug concentrations and optimal drug dosage of new compounds for systemic treatment of BMs to reduce the risk of using ineffective drugs (waste of opportunity) and missing effective drugs (loss of opportunity) for efficient and evidence-based planning of early phase II trials (see figure 4).

Identification of genetic/molecular signature

Several genetic signatures have been characterised in solid tumours, which are not only relevant prognostically but determine the oncological management.[62] However, little is known about whether BMs share the signature of the primary tumour and whether multiple BMs are of clonal origin with the same molecular pattern. Especially in cases where the molecular profile determines the therapeutic management, it would be mandatory to know the profile of the BMs as well. Assuming the BMs and primary lesion would not necessarily match in terms of their molecular signature, at least a stereotactic biopsy of the BMs would be necessary to tailor the treatment. The strive to personalise cancer treatment, also for BMs, might increase the demand for tissue analysis of BMs even in the case of a known primary lesion. Molecular analysis of CSF samples has been shown to be a useful tool to identify clinically relevant genomic alterations, including aberrations not found in primary

Highlights and recommendations of the roundtable discussion

Biology and molecular alterations of non-small cell lung cancer (NSCLC) brain metastases

- Detailed studies of the biology have provided molecular mediators of critical processes in the metastatic colonisation of the brain that could offer novel avenues for translational efforts.
- The naive brain microenvironment can eliminate multiple brain metastasis (BM) cells by activating innate immunity mechanisms. However, successful BM cells have developed ways to avoid them and progress in the metastatic cascade by colonising the crucial perivascular niche in the brain.
- A critical process to initiate BMs involves the ability to co-opt pre-existing blood vessels, or grow by angiogenesis. Both mechanisms imply opportunities to target the growth of non-clinically detectable BMs in a preventive scenario.
- Exploiting the functional contribution of genomic alterations identified in human next-generation studies on BMs will be critical to evaluate the potential of targeting actionable mutations. In addition, these alterations could be used to track BMs using liquid biopsies.
- Given the specificity of the biology of BMs, the importance of the microenvironment in the progression of the disease and its potential to become a novel therapeutic target has started to be evaluated and pioneering clinical trials are ongoing.
- Improvement of experimental models that include clinically relevant situations (ie, radiation, neurosurgery, targeted therapies, specific molecular alterations, spontaneous models of metastases, studies in animals with intact immune system) is critical to learn more about the biology of BMs, and to provide a foundation for successful translation into clinical practice.

The relevance of the blood–brain barrier (BBB) for medical treatment of NSCLC BMs

- Many open questions about the BBB and BMs remain, but it is not justified always to expect a limited BBB penetration and a lack of meaningful central nervous system (CNS) activity for any given drug without testing it. Recent data suggest that even large molecules like therapeutic antibodies are able to penetrate the BBB in patients with BMs, at least to some extent.

Treatment of NSCLC BMs

- CNS metastases constitute a major problem in NSCLC, particularly in patients with ALK rearrangements and even more so in those with ALK rearrangements pretreated with crizotinib. The CNS seems to act as a sanctuary for the emergence of metastases. In such situations, treatments with ALK-rearrangement-directed tyrosine kinase inhibitors (TKIs) like ceritinib, alectinib or brigatinib (although each with different toxicity profiles) represent a viable and effective treatment option. However, the question of an appropriate treatment sequence emerges and this will have to be the topic of future clinical investigations.
- The development of epidermal growth factor receptor (EGFR) TKIs has now reached third-generation agents with promising early results. Preclinical and clinical evidence shows them to be more effective, having a better blood brain penetration and the potential to overcome EGFR TKI resistance. Clinically, osimertinib has greater efficacy than platinum/pemetrexed in patients with T790M-positive NSCLC, including those with CNS metastases in a second-line setting. AZD 3759 has primarily been designed for crossing the BBB.
- The combination of radiotherapy and TKIs or immunotherapy is a promising treatment for NSCLC BMs but needs to be developed and validated in biologically driven clinical trials in terms of dose and timing. The trials should be associated with neurocognitive studies as well as metabolic imaging to distinguish progression from pseudo-progression.
- The surrounding tissue of NSCLC BMs represents an important target in the resection as well as in the medical treatment and radiosurgery/radiotherapy of such tumours. In surgery, a ‘microscopic total resection’ with additional safe removal of the surrounding brain tissue of about 5 mm in non-eloquent BMs showed improvement of the local control rate. Intraoperative markers for selective visualisation of tumour infiltration into the surrounding brain tissue have to be further investigated.

Neurosurgical interventions for the analysis of drug concentrations and biomarkers

- Window-of-opportunity studies could be a promising tool to obtain information about inter-individual variation of drug concentrations and optimal drug dosage of new compounds for systemic treatment of BMs. They could reduce the risk of using ineffective drugs (waste of opportunity) and missing effective drugs (loss of opportunity) for an efficient and evidence-based planning of early phase II trials.
- The strive to personalise cancer treatment, also for BMs, might increase the demand for tissue analysis of BMs even in the case of a known primary lesion.

tumours in patients with BMs.[130] Thus, liquid biopsies from CSF may improve personalised therapy of patients with BMs.

CONCLUSION

The roundtable discussion highlighted the urgent need to define better treatments for prophylaxis and treatment of BMs in patients with NSCLC. The growing insights into the pathobiology of BMs and molecular treatment targets lead to novel therapy approaches that need to be tested in clinical trials enrolling patients with BMs.

Author affiliations
[1]Clinical Division of Oncology, Department of Medicine I, Comprehensive Cancer Centre, Medical University Vienna – General Hospital, Vienna, Austria
[2]Neurology Clinic and National Center for Tumor Diseases, University Hospital Heidelberg, Heidelberg, Germany
[3]Clinical Cooperation Unit Neuro-oncology, German Cancer Consortium (DKTK), German Cancer Research Center (DKFZ), Heidelberg, Germany
[4]Brain Metastasis Group, Spanish National Cancer Research Centre (CNIO), Madrid, Spain
[5]Medical Faculty Mannheim, University of Heidelberg, Mannheim, Baden-Württemberg, Germany
[6]Radiation Oncology Department, Radiobiology team 11, UMR1037 INSERM, Institut Universitaire du Cancer de Toulouse Oncopole, Centre de Recherche contre le Cancer, Toulouse, France
[7]Department of Neurosurgery, Medical University of Vienna (MUV), Vienna, Austria
[8]Department of Neurosurgery, University of California San Francisco (UCSF), San Francisco, USA
[9]Comprehensive Cancer Center–Central Nervous System Tumours Unit (CCC-CNS), Medical University Vienna (MUV), Vienna, Austria
[10]Department of Neurosurgery, Ludwig-Maximilians University, Munich-Grosshadern, Germany and German Cancer Consortium (DKTK) at the German Cancer Research Centre (DKFZ), Heidelberg, Germany

Funding This initiative is sponsored by AstraZeneca through the provision of an unrestricted educational grant. AstraZeneca has had no influence over the content other than a review of the paper for medical accuracy. The participants/authors received an honorarium for their participation from BMJ.

Competing interests MP: Research support from Boehringer-Ingelheim, GlaxoSmithKline, Merck Sharp and Dohme and Roche and honoraria for lectures, consultation or advisory board participation from Bristol-Myers Squibb, Novartis, Gerson Lehrman Group (GLG), CMC Contrast, GlaxoSmithKline, Mundipharma, Roche, AstraZeneca and AbbVie. FW: Research support from Boehringer Ingelheim, Genentech and Roche. Honoraria for lectures, consultation and advisory board participation from UCB, Roche and Boehringer Ingelheim. CM: Honoraria from Lilly and Boehringer Ingelheim. EM: Research support from AstraZeneca, Merck KGaA, advisory board participation from Merck KGaA. CZ: Honoraria from Ariad, Novartis, Boehringer Ingelheim, Roche and AstraZeneca.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1. Barnholtz-Sloan JS, Sloan AE, Davis FG, *et al*. Incidence proportions of brain metastases in patients diagnosed (1973 to 2001) in the metropolitan Detroit cancer surveillance system. *J Clin Oncol* 2004;22:2865–72.
2. Kohler BA, Ward E, McCarthy BJ, *et al*. Annual report to the nation on the status of cancer, 1975-2007, featuring tumors of the brain and other nervous system. *J Natl Cancer Inst* 2011;103:714–36.
3. Toyokawa G, Seto T, Takenoyama M, *et al*. Insights into brain metastasis in patients with ALK+ lung cancer: is the brain truly a sanctuary? *Cancer Metastasis Rev* 2015;34:797–805.
4. Mamon HJ, Yeap BY, Jänne PA, *et al*. 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;23:1530–7.
5. Felip E, Orlov S, Park K, *et al*. ASCEND-3: A single-arm, open-label, multicenter phase II study of ceritinib in ALKi-naïve adult patients (pts) with ALK-rearranged (ALK+) non-small cell lung cancer (NSCLC). *J Clin Oncol* 2015;33.
6. Gahr S, Stoehr R, Geissinger E, *et al*. EGFR mutational status in a large series of Caucasian European NSCLC patients: data from daily practice. *Br J Cancer* 2013;109:1821–8.
7. Jiang T, Su C, Li X, *et al*. EGFR TKIs plus WBRT demonstrated no survival benefit other than that of TKIs alone in patients with NSCLC and EGFR mutation and brain metastases. *J Thorac Oncol* 2016;11:1718–28.
8. Doebele RC, Lu X, Sumey C, *et al*. Oncogene status predicts patterns of metastatic spread in treatment-naive nonsmall cell lung cancer. *Cancer* 2012;118:4502–11.
9. Bhatt VR, Kedia S, Kessinger A, *et al*. Brain metastasis in patients with non-small-cell lung cancer and epidermal growth factor receptor mutations. *J Clin Oncol* 2013;31:3162–4.
10. Heon S, Yeap BY, Britt GJ, *et al*. Development of central nervous system metastases in patients with advanced non-small cell lung cancer and somatic EGFR mutations treated with gefitinib or erlotinib. *Clin Cancer Res* 2010;16:5873–82.
11. Gaspar L, Scott C, Rotman M, *et al*. Recursive partitioning analysis (RPA) of prognostic factors in three Radiation Therapy Oncology Group (RTOG) brain metastases trials. *Int J Radiat Oncol Biol Phys* 1997;37:745–51.
12. Lagerwaard FJ, Levendag PC, Nowak PJ, *et al*. Identification of prognostic factors in patients with brain metastases: a review of 1292 patients. *Int J Radiat Oncol Biol Phys* 1999;43:795–803.
13. Yates JW, Chalmer B, McKegney FP. Evaluation of patients with advanced cancer using the Karnofsky performance status. *Cancer* 1980;45:2220–4.
14. Fife KM, Colman MH, Stevens GN, *et al*. Determinants of outcome in melanoma patients with cerebral metastases. *J Clin Oncol* 2004;22:1293–300.
15. Bos PD, Zhang XH, Nadal C, *et al*. Genes that mediate breast cancer metastasis to the brain. *Nature* 2009;459:1005–9.
16. Li B, Wang C, Zhang Y, *et al*. Elevated PLGF contributes to small-cell lung cancer brain metastasis. *Oncogene* 2013;32:2952–62.
17. Sevenich L, Bowman RL, Mason SD, *et al*. Analysis of tumour- and stroma-supplied proteolytic networks reveals a brain-metastasis-promoting role for cathepsin S. *Nat Cell Biol* 2014;16:876–88.
18. Jilaveanu LB, Parisi F, Barr ML, *et al*. PLEKHA5 as a biomarker and potential mediator of melanoma brain metastasis. *Clin Cancer Res* 2015;21:2138–47.
19. Kienast Y, von Baumgarten L, Fuhrmann M, *et al*. Real-time imaging reveals the single steps of brain metastasis formation. *Nat Med* 2010;16:116–22.
20. Louie E, Chen XF, Coomes A, *et al*. Neurotrophin-3 modulates breast cancer cells and the microenvironment to promote the growth of breast cancer brain metastasis. *Oncogene* 2013;32:4064–77.
21. Valiente M, Obenauf AC, Jin X, *et al*. Serpins promote cancer cell survival and vascular co-option in brain metastasis. *Cell* 2014;156:1002–16.
22. Winkler F. Hostile takeover: how tumours hijack pre-existing vascular environments to thrive. *J Pathol* 2017;242:267–72.
23. Carbonell WS, Ansorge O, Sibson N, *et al*. The vascular basement membrane as 'soil' in brain metastasis. *PLoS One* 2009;4:e5857.
24. Ghajar CM, Peinado H, Mori H, *et al*. The perivascular niche regulates breast tumour dormancy. *Nat Cell Biol* 2013;15:807–17.
25. Rafii S, Butler JM, Ding BS. Angiocrine functions of organ-specific endothelial cells. *Nature* 2016;529:316–25.
26. Malladi S, Macalinao DG, Jin X, *et al*. Metastatic latency and immune evasion through autocrine inhibition of WNT. *Cell* 2016;165:45–60.
27. Gao H, Chakraborty G, Zhang Z, *et al*. Multi-organ site metastatic reactivation mediated by non-canonical discoidin domain receptor 1 signaling. *Cell* 2016;166:47–62.

28. Ilhan-Mutlu A, Osswald M, Liao Y, *et al*. Bevacizumab prevents brain metastases formation in lung adenocarcinoma. *Mol Cancer Ther* 2016;15:702–10.
29. Berghoff AS, Rajky O, Winkler F, *et al*. Invasion patterns in brain metastases of solid cancers. *Neuro Oncol* 2013;15:1664–72.
30. Siam L, Bleckmann A, Chaung HN, *et al*. The metastatic infiltration at the metastasis/brain parenchyma-interface is very heterogeneous and has a significant impact on survival in a prospective study. *Oncotarget* 2015;6:29254–67.
31. Brastianos PK, Carter SL, Santagata S, *et al*. Genomic characterization of brain metastases reveals branched evolution and potential therapeutic targets. *Cancer Discov* 2015;5:1164–77.
32. Paik PK, Shen R, Won H, *et al*. Next-generation sequencing of stage IV squamous cell lung cancers reveals an association of PI3K aberrations and evidence of clonal heterogeneity in patients with brain metastases. *Cancer Discov* 2015;5:610–21.
33. Saunus JM, Quinn MC, Patch AM, *et al*. Integrated genomic and transcriptomic analysis of human brain metastases identifies alterations of potential clinical significance. *J Pathol* 2015;237:363–78.
34. De Mattos-Arruda L, Mayor R, Ng CK, Ck N, *et al*. Cerebrospinal fluid-derived circulating tumour DNA better represents the genomic alterations of brain tumours than plasma. *Nat Commun* 2015;6:8839.
35. Lee JY, Park K, Lim SH, *et al*. Mutational profiling of brain metastasis from breast cancer: matched pair analysis of targeted sequencing between brain metastasis and primary breast cancer. *Oncotarget* 2015;6:43731–42.
36. Pentsova EI, Shah RH, Tang J, *et al*. Evaluating cancer of the central nervous system through next-generation sequencing of cerebrospinal fluid. *J Clin Oncol* 2016;34:2404–15.
37. Priedigkeit N, Hartmaier RJ, Chen Y, *et al*. Intrinsic subtype switching and acquired ERBB2/HER2 amplifications and mutations in breast cancer brain metastases. *JAMA Oncol* 2017;3:666–71.
38. Lin Q, Balasubramanian K, Fan D, *et al*. Reactive astrocytes protect melanoma cells from chemotherapy by sequestering intracellular calcium through gap junction communication channels. *Neoplasia* 2010;12:748–54.
39. Kim SJ, Kim JS, Park ES, *et al*. Astrocytes upregulate survival genes in tumor cells and induce protection from chemotherapy. *Neoplasia* 2011;13:286–98.
40. Stoletov K, Strnadel J, Zardouzian E, *et al*. Role of connexins in metastatic breast cancer and melanoma brain colonization. *J Cell Sci* 2013;126:904–13.
41. Kim SW, Choi HJ, Lee HJ, *et al*. Role of the endothelin axis in astrocyte-and endothelial cell-mediated chemoprotection of cancer cells. *Neuro Oncol* 2014;16:1585–98.
42. Chen Q, Boire A, Jin X, *et al*. Carcinoma-astrocyte gap junctions promote brain metastasis by cGAMP transfer. *Nature* 2016;533:493–8.
43. Steeg PS, Camphausen KA, Smith QR. Brain metastases as preventive and therapeutic targets. *Nat Rev Cancer* 2011;11:352–63.
44. Palmieri D, Chambers AF, Felding-Habermann B, *et al*. The biology of metastasis to a sanctuary site. *Clin Cancer Res* 2007;13:1656–62.
45. Gerstner ER, Fine RL. Increased permeability of the blood-brain barrier to chemotherapy in metastatic brain tumors: establishing a treatment paradigm. *J Clin Oncol* 2007;25:2306–12.
46. Fortin D. The blood-brain barrier: its influence in the treatment of brain tumors metastases. *Curr Cancer Drug Targets* 2012;12:247–59.
47. Yu YJ, Zhang Y, Kenrick M, *et al*. Boosting brain uptake of a therapeutic antibody by reducing its affinity for a transcytosis target. *Sci Transl Med* 2011:3:ra44.
48. Daneman R. The blood-brain barrier in health and disease. *Ann Neurol* 2012;72:648–72.
49. Couch JA, Yu YJ, Zhang Y, *et al*. Addressing safety liabilities of TfR bispecific antibodies that cross the blood-brain barrier. *Sci Transl Med* 2013;5:183ra57–12.
50. Gaudino S, Di Lella GM, Russo R, *et al*. Magnetic resonance imaging of solitary brain metastases: main findings of nonmorphological sequences. *Radiol Med* 2012;117:1225–41.
51. Fidler IJ, Yano S, Zhang RD, *et al*. The seed and soil hypothesis: vascularisation and brain metastases. *Lancet Oncol* 2002;3:53–7.
52. Lockman PR, Mittapalli RK, Taskar KS, *et al*. Heterogeneous blood-tumor barrier permeability determines drug efficacy in experimental brain metastases of breast cancer. *Clin Cancer Res* 2010;16:5664–78.
53. Percy DB, Ribot EJ, Chen Y, *et al*. In vivo characterization of changing blood-tumor barrier permeability in a mouse model of breast cancer metastasis: a complementary magnetic resonance imaging approach. *Invest Radiol* 2011;46:718–25.
54. Pitz MW, Desai A, Grossman SA, *et al*. Tissue concentration of systemically administered antineoplastic agents in human brain tumors. *J Neurooncol* 2011;104:629–38.
55. Morikawa A, Peereboom DM, Thorsheim HR, *et al*. Capecitabine and lapatinib uptake in surgically resected brain metastases from metastatic breast cancer patients: a prospective study. *Neuro Oncol* 2015;17:289–95.
56. Lewis Phillips GD, Nishimura MC, Lacap JA, *et al*. Trastuzumab uptake and its relation to efficacy in an animal model of HER2-positive breast cancer brain metastasis. *Breast Cancer Res Treat* 2017;164:581–91.
57. Osswald M, Blaes J, Liao Y, *et al*. Impact of blood-brain barrier integrity on tumor growth and therapy response in brain metastases. *Clin Cancer Res* 2016;22:6078–87.
58. Bartsch R, Berghoff AS, Vogl U, *et al*. Activity of T-DM1 in Her2-positive breast cancer brain metastases. *Clin Exp Metastasis* 2015;32:729–37.
59. Salphati L, Heffron TP, Alicke B, *et al*. Targeting the PI3K pathway in the brain-efficacy of a PI3K inhibitor optimized to cross the blood-brain barrier. *Clin Cancer Res* 2012;18:6239–48.
60. Preusser M, Capper D, Ilhan-Mutlu A, *et al*. Brain metastases: pathobiology and emerging targeted therapies. *Acta Neuropathol* 2012;123:205–22.
61. Barlesi F, Gervais R, Lena H, *et al*. Pemetrexed and cisplatin as first-line chemotherapy for advanced non-small-cell lung cancer (NSCLC) with asymptomatic inoperable brain metastases: a multicenter phase II trial (GFPC 07-01). *Ann Oncol* 2011;22:2466–70.
62. Soffietti R, Abacioglu U, Baumert B, *et al*. Diagnosis and treatment of brain metastases from solid tumors: guidelines from the European Association of Neuro-Oncology (EANO). *Neuro Oncol* 2017;19:162–74.
63. Mahajan A, Ahmed S, McAleer MF, *et al*. Post-operative stereotactic radiosurgery versus observation for completely resected brain metastases: a single-centre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1040–8.
64. Brown PD, Ballman KV, Cerhan JH, *et al*. Postoperative stereotactic radiosurgery compared with whole brain radiotherapy for resected metastatic brain disease (NCCTG N107C/CEC·3): a multicentre, randomised, controlled, phase 3 trial. *Lancet Oncol* 2017;18:1049–60.
65. Brown PD, Jaeckle K, Ballman KV, *et al*. Effect of radiosurgery alone vs radiosurgery with whole brain radiation therapy on cognitive function in patients with 1 to 3 brain metastases: a randomized clinical trial. *JAMA* 2016;316:401–9.
66. Aoyama H, Tago M, Shirato H. Stereotactic radiosurgery with or without whole-brain radiotherapy for brain metastases: secondary analysis of the JROSG 99-1 randomized clinical trial. *JAMA Oncol* 2015;1:457–64.
67. Gondi V, Pugh SL, Tome WA, *et al*. Preservation of memory with conformal avoidance of the hippocampal neural stem-cell compartment during whole-brain radiotherapy for brain metastases (RTOG 0933): a phase II multi-institutional trial. *J Clin Oncol* 2014;32:3810–6.
68. Brown PD, Pugh S, Laack NN, *et al*. Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: a randomized, double-blind, placebo-controlled trial. *Neuro Oncol* 2013;15:1429–37.
69. Yamamoto M, Serizawa T, Shuto T, *et al*. Stereotactic radiosurgery for patients with multiple brain metastases (JLGK0901): a multi-institutional prospective observational study. *Lancet Oncol* 2014;15:387–95.
70. Yamamoto M, Serizawa T, Higuchi Y, *et al*. A multi-institutional prospective observational study of stereotactic radiosurgery for patients with multiple brain metastases (jlgk0901 study update): Irradiation-related complications and long-term maintenance of mini-mental state examination scores. *Int J Radiat Oncol Biol Phys* 2017;99:31–40.
71. Mulvenna P, Nankivell M, Barton R, *et al*. Dexamethasone and supportive care with or without whole brain radiotherapy in treating patients with non-small cell lung cancer with brain metastases unsuitable for resection or stereotactic radiotherapy (QUARTZ): results from a phase 3, non-inferiority, randomised trial. *Lancet* 2016;388:2004–14.
72. Mehta MP, Rodrigus P, Terhaard CH, *et al*. Survival and neurologic outcomes in a randomized trial of motexafin gadolinium and whole-brain radiation therapy in brain metastases. *J Clin Oncol* 2003;21:2529–36.

73. DeAngelis LM, Currie VE, Kim JH, *et al*. The combined use of radiation therapy and lonidamine in the treatment of brain metastases. *J Neurooncol* 1989;7:241–7.
74. Eyre HJ, Ohlsen JD, Frank J, *et al*. Randomized trial of radiotherapy versus radiotherapy plus metronidazole for the treatment metastatic cancer to brain. A southwest oncology group study. *J Neurooncol* 1984;2:325–30.
75. Komarnicky LT, Phillips TL, Martz K, *et al*. A randomized phase III protocol for the evaluation of misonidazole combined with radiation in the treatment of patients with brain metastases (RTOG-7916). *Int J Radiat Oncol Biol Phys* 1991;20:53–8.
76. Phillips TL, Scott CB, Leibel SA, *et al*. Results of a randomized comparison of radiotherapy and bromodeoxyuridine with radiotherapy alone for brain metastases: report of RTOG trial 89-05. *Int J Radiat Oncol Biol Phys* 1995;33:339–48.
77. Suh JH, Stea B, Nabid A, *et al*. Phase III study of efaproxiral as an adjunct to whole-brain radiation therapy for brain metastases. *J Clin Oncol* 2006;24:106–14.
78. Mornex F, Thomas L, Mohr P, *et al*. A prospective randomized multicentre phase III trial of fotemustine plus whole brain irradiation versus fotemustine alone in cerebral metastases of malignant melanoma. *Melanoma Res* 2003;13:97–103.
79. Postmus PE, Haaxma-Reiche H, Smit EF, *et al*. Treatment of brain metastases of small-cell lung cancer: comparing teniposide and teniposide with whole-brain radiotherapy-a phase III study of the European organization for the research and treatment of cancer lung cancer cooperative group. *J Clin Oncol* 2000;18:3400–8.
80. Ushio Y, Arita N, Hayakawa T, *et al*. Chemotherapy of brain metastases from lung carcinoma: a controlled randomized study. *Neurosurgery* 1991;28:201–5.
81. Antonadou D, Paraskevaidis M, Sarris G, *et al*. Phase II randomized trial of temozolomide and concurrent radiotherapy in patients with brain metastases. *J Clin Oncol* 2002;20:3644–50.
82. Verger E, Gil M, Yaya R, *et al*. Temozolomide and concomitant whole brain radiotherapy in patients with brain metastases: a phase II randomized trial. *Int J Radiat Oncol Biol Phys* 2005;61:185–91.
83. Edelman MJ, Belani CP, Socinski MA, *et al*. Outcomes associated with brain metastases in a three-arm phase III trial of gemcitabine-containing regimens versus paclitaxel plus carboplatin for advanced non-small cell lung cancer. *J Thorac Oncol* 2010;5:110–6.
84. Baik CS, Chamberlain MC, Chow LQ. Targeted therapy for brain metastases in EGFR-mutated and ALK-rearranged non-small-cell lung cancer. *J Thorac Oncol* 2015;10:1268–78.
85. Togashi Y, Masago K, Masuda S, *et al*. Cerebrospinal fluid concentration of gefitinib and erlotinib in patients with non-small cell lung cancer. *Cancer Chemother Pharmacol* 2012;70:399–405.
86. Mok TS, Wu YL, Thongprasert S, *et al*. Gefitinib or carboplatin-paclitaxel in pulmonary adenocarcinoma. *N Engl J Med* 2009;361:947–57.
87. Rosell R, Carcereny E, Gervais R, *et al*. Erlotinib versus standard chemotherapy as first-line treatment for European patients with advanced EGFR mutation-positive non-small-cell lung cancer (EURTAC): a multicentre, open-label, randomised phase 3 trial. *Lancet Oncol* 2012;13:239–46.
88. Sequist LV, Yang JC, Yamamoto N, *et al*. Phase III study of afatinib or cisplatin plus pemetrexed in patients with metastatic lung adenocarcinoma with EGFR mutations. *J Clin Oncol* 2013;31:3327–34.
89. Iuchi T, Shingyoji M, Sakaida T, *et al*. Phase II trial of gefitinib alone without radiation therapy for Japanese patients with brain metastases from EGFR-mutant lung adenocarcinoma. *Lung Cancer* 2013;82:282–7.
90. Porta R, Sánchez-Torres JM, Paz-Ares L, *et al*. Brain metastases from lung cancer responding to erlotinib: the importance of EGFR mutation. *Eur Respir J* 2011;37:624–31.
91. Campas C, Castañer R, Bolos J. BIBW-2992. Dual EGFR/HER2 inhibitor, oncolytic. *Drugs Future* 2008;33:649.
92. Hoffknecht P, Tufman A, Wehler T, *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;10:156–63.
93. Schuler M, Wu YL, Hirsh V, *et al*. First-line afatinib versus chemotherapy in patients with non-small cell lung cancer and common epidermal growth factor receptor gene mutations and brain metastases. *J Thorac Oncol* 2016;11:380–90.
94. Ballard P, Yates JW, Yang Z, *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;22:5130–40.
95. Jänne PA, Yang JC, Kim DW, *et al*. AZD9291 in EGFR inhibitor-resistant non-small-cell lung cancer. *N Engl J Med* 2015;372:1689–99.
96. Ahn MJ, Kim DW, Kim TM, *et al*. Phase I study of AZD3759, a CNS penetrable EGFR inhibitor, for the treatment of non-small-cell lung cancer (NSCLC) with brain metastasis (BM) and leptomeningeal metastasis (LM). *J Clin Oncol34* 2016. (suppl; abstr 9003).
97. Kim DW, Yang JC-H, Chen K, *et al*. AZD3759, an EGFR inhibitor with blood brain barrier (BBB) penetration for the treatment of non-small cell lung cancer (NSCLC) with brain metastasis (BM): Preclinical evidence and clinical cases. *J Clin Oncol33* 2015. (suppl; abstr 8016).
98. Solomon BJ, Mok T, Kim DW, *et al*. First-line crizotinib versus chemotherapy in ALK-positive lung cancer. *N Engl J Med* 2014;371:2167–77.
99. Camidge DR, Bang YJ, Kwak EL, *et al*. Activity and safety of crizotinib in patients with *ALK*-positive non-small-cell lung cancer: updated results from a phase 1 study. *Lancet Oncol* 2012;13:1011–9.
100. Shaw AT, Ou SH, Bang YJ, *et al*. Crizotinib in ROS1-rearranged non-small-cell lung cancer. *N Engl J Med* 2014;371:1963–71.
101. Weickhardt AJ, Scheier B, Burke JM, *et al*. Local ablative therapy of oligoprogressive disease prolongs disease control by tyrosine kinase inhibitors in oncogene-addicted non-small-cell lung cancer. *J Thorac Oncol* 2012;7:1807–14.
102. Doebele RC, Pilling AB, Aisner DL, *et al*. Mechanisms of resistance to crizotinib in patients with ALK gene rearranged non-small cell lung cancer. *Clin Cancer Res* 2012;18:1472–82.
103. Katayama R, Shaw AT, Khan TM, *et al*. Mechanisms of acquired crizotinib resistance in ALK-rearranged lung Cancers. *Sci Transl Med* 2012;4:120ra17.
104. Ou SH, Ahn JS, De Petris L, *et al*. Alectinib in crizotinib-refractory alk-rearranged non-small-cell lung cancer: a phase ii global study. *J Clin Oncol* 2016;34:661–8.
105. Gettinger SN, Kim D, Tiseo M, *et al*, 2016. *Brigatinib activity in patients with ALK+ NSCLC and intracranial CNS metastases in two clinical trials. 17th World Conference on Lung Cancer*. Vienna, Austria: International Association for the Study of Lung Cancer
106. Peters S, Camidge DR, Shaw AT, *et al*. Alectinib versus crizotinib in untreated ALK-positive non-small-cell lung cancer. *N Engl J Med* 2017;377:829–38.
107. Kocher M, Soffietti R, Abacioglu U, *et al*. Adjuvant whole-brain radiotherapy versus observation after radiosurgery or surgical resection of one to three cerebral metastases: results of the EORTC 22952-26001 study. *J Clin Oncol* 2011;29:134–41.
108. Soffietti R, Kocher M, Abacioglu UM, *et al*. A European organisation for research and treatment of cancer phase III trial of adjuvant whole-brain radiotherapy versus observation in patients with one to three brain metastases from solid tumors after surgical resection or radiosurgery: quality-of-life results. *J Clin Oncol* 2013;31:65–72.
109. Rao G, Ahmed S, Hess K, *et al*. 215 Postoperative stereotactic radiosurgery vs observation for completely resected brain metastases: results of a prospective randomized study. *Neurosurgery* 2016;63:184.
110. Jonathan EC, Bernhard EJ, McKenna WG, *et al*. How does radiation kill cells? *Curr Opin Chem Biol* 1999;3:77–83.
111. Garcia-Barros M, Paris F, Cordon-Cardo C, *et al*. Tumor response to radiotherapy regulated by endothelial cell apoptosis. *Science* 2003;300:1155–9.
112. Lee Y, Auh SL, Wang Y, *et al*. Therapeutic effects of ablative radiation on local tumor require CD8+ T cells: changing strategies for cancer treatment. *Blood* 2009;114:589–95.
113. D'Souza NM, Fang P, Logan J, *et al*. Combining radiation therapy with immune checkpoint blockade for central nervous system malignancies. *Front Oncol* 2016;6:212.
114. Deng L, Liang H, Burnette B, *et al*. Irradiation and anti-PD-L1 treatment synergistically promote antitumor immunity in mice. *J Clin Invest* 2014;124:687–95.
115. Luo S, Chen L, Chen X, *et al*. Evaluation on efficacy and safety of tyrosine kinase inhibitors plus radiotherapy in NSCLC patients with brain metastases. *Oncotarget* 2015;6:16725–34.
116. Doherty MK, Korpanty GJ, Tomasini P, *et al*. Treatment options for patients with brain metastases from EGFR/ALK-driven lung cancer. *Radiother Oncol* 2017;123:195–202.
117. Zhu Q, Sun Y, Cui Y, *et al*. Clinical outcome of tyrosine kinase inhibitors alone or combined with radiotherapy for brain metastases from epidermal growth factor receptor (EGFR) mutant non small cell lung cancer (NSCLC). *Oncotarget* 2017;8:13304–11.
118. Magnuson WJ, Lester-Coll NH, Wu AJ, *et al*. Management of brain metastases in tyrosine kinase inhibitor-naïve epidermal growth factor receptor-mutant non-small-cell lung cancer: a retrospective multi-institutional analysis. *J Clin Oncol* 2017;35:1070–7.

119. Choong ES, Lo S, Drummond M, *et al*. Survival of patients with melanoma brain metastasis treated with stereotactic radiosurgery and active systemic drug therapies. *Eur J Cancer* 2017;75:169–78.
120. Ahmed KA, Kim S, Arrington J, *et al*. Outcomes targeting the PD-1/PD-L1 axis in conjunction with stereotactic radiation for patients with non-small cell lung cancer brain metastases. *J Neurooncol* 2017;133:331–8.
121. Franceschini D, Franzese C, Navarria P, *et al*. Radiotherapy and immunotherapy: Can this combination change the prognosis of patients with melanoma brain metastases? *Cancer Treat Rev* 2016;50:1–8.
122. Kiess AP, Wolchok JD, Barker CA, *et al*. Stereotactic radiosurgery for melanoma brain metastases in patients receiving ipilimumab: safety profile and efficacy of combined treatment. *Int J Radiat Oncol Biol Phys* 2015;92:368–75.
123. Qian JM, Yu JB, Kluger HM, *et al*. Timing and type of immune checkpoint therapy affect the early radiographic response of melanoma brain metastases to stereotactic radiosurgery. *Cancer* 2016;122:3051–8.
124. Patchell RA, Tibbs PA, Walsh JW, *et al*. A randomized trial of surgery in the treatment of single metastases to the brain. *N Engl J Med* 1990;322:494–500.
125. Enders F, Geisenberger C, Jungk C, *et al*. Prognostic factors and long-term survival in surgically treated brain metastases from non-small cell lung cancer. *Clin Neurol Neurosurg* 2016;142:72–80.
126. Yoo H, Kim YZ, Nam BH, *et al*. Reduced local recurrence of a single brain metastasis through microscopic total resection. *J Neurosurg* 2009;110:730–6.
127. Kamp MA, Grosser P, Felsberg J, *et al*. 5-aminolevulinic acid (5-ALA)-induced fluorescence in intracerebral metastases: a retrospective study. *Acta Neurochir* 2012;154:223–8.
128. Torres S, Maralani P, Verma S. Activity of T-DM1 in HER-2 positive central nervous system breast cancer metastases. *BMJ Case Rep* 2014;2014:bcr2014205680.
129. Berghoff AS, Wolpert F, Holland-Letz T, *et al*. Combining standard clinical blood values for improving survival prediction in patients with newly diagnosed brain metastases-development and validation of the LabBM score. *Neuro Oncol* 2017;19: [Epub ahead of print 17 Jan 2017].
130. Pentsova EI, Shah RH, Tang J, *et al*. Evaluating cancer of the central nervous system through next-generation sequencing of Cerebrospinal Fluid. *J Clin Oncol* 2016;34:2404–15.