CONGRESS OF NEUROLOGICAL SURGEONS SYSTEMATIC REVIEW AND EVIDENCE-BASED GUIDELINE ON THE ROLE OF EMERGING AND INVESTIGATIONAL THERAPIES FOR THE TREATMENT OF ADULTS WITH METASTATIC BRAIN TUMORS

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Abbreviations

BM: Brain metastases

CNS: Central nervous system

CSF: Cerebrospinal fluid

EGFR: Epidermal growth factor receptor

HIFU: High-intensity focused ultrasound

LITT: Laser interstitial thermal therapy

MRI: Magnetic resonance imaging

MTD: Maximum tolerated dose

NSCLC: Non-small cell lung cancer

OS: Overall survival

PDT: Photodynamic therapy

PFS: Progression-free survival

RCC: Renal cell carcinoma

SBT: Stereotactic brachytherapy

SRS: Stereotactic radiosurgery

TKI: Tyrosine kinase inhibitors

VEGF: Vascular endothelial growth factor

WBRT: Whole brain radiation therapy

WT: Wild type

No part of this manuscript has been published or submitted for publication elsewhere.

ABSTRACT

Question

What evidence is available regarding emerging and investigational treatment options for metastatic brain tumors?

Target Population

Adult patients with brain metastases

Recommendations

High Intensity Focused Ultrasound

There is insufficient evidence to make a recommendation regarding the use of high intensity focused ultrasound (HIFU) for the treatment of patients with brain metastases.

Laser Interstitial Thermal Therapy

There is insufficient evidence to make a recommendation regarding the routine use of laser interstitial thermal therapy (LITT), aside from use as part of approved clinical trials.

Radiation Sensitizers

Level 1: The use of temozolomide as a radiation sensitizer is not recommended in the setting of whole brain radiation therapy (WBRT) for patients with breast cancer brain metastases.

Level 1: The use of chloroquine as radiation sensitizer is not recommended in the setting of WBRT for patients with brain metastases.

There is insufficient evidence to make a recommendation regarding the routine use of radiation sensitizers, such as motexafin-gadolinium, sodium nitrite, temozolomide, or chloroquine, in other clinical settings for patients with brain metastases.

Interstitial Modalities

There is insufficient evidence to make a recommendation regarding the routine use of existing local therapies, such as interstitial chemotherapy, brachytherapy, or other local modalities, aside from their use in approved clinical trials.

Immune Modulators

There is insufficient evidence to make a recommendation regarding the use of immune therapy for brain metastases.

Molecular Targeted Agents

Level 1: The use of afatinib is not recommended in patients with brain metastasis due to breast cancer.

There is insufficient evidence to make recommendations regarding:

- the use of epidermal growth factor receptor inhibitors erlotinib and gefitinib in patients with brain metastasis due to non-small cell lung cancer;
- the use of BRAF inhibitors dabrafenib and vemurafenib in the treatment of patients with brain metastases due to metastatic melanoma;
- the use of HER2 agents trastuzumab and lapatinib to treat patients with brain metastases due to metastatic breast cancer;

- the use of vascular endothelial growth factor agents bevacizumab, sunitinib, and sorafenib in the treatment of patients with solid tumor brain metastases.

INTRODUCTION

Rationale

Brain metastases associated with systemic cancer remain challenging to treat. Current standard treatment modalities, including surgery and radiation, cannot be applied to all patients, and are not uniformly successful when applied. Therefore, novel treatment strategies are necessary.

Other publications in this guideline series provide updates on standard treatment modalities, such as surgery and radiation. The objective of this paper is to review the available clinical research regarding non-standard or 'emerging' therapies. Therapies considered 'emerging' are in the investigational stage and, generally, are not currently in use aside from clinical trials.

Objectives

New treatments for brain metastases aim to achieve control of the disease while minimizing toxicity and neurologic morbidity. Current clinical research that focuses on new surgical techniques and systemic agents is reviewed in this guideline. The specific objectives of this paper are to critically evaluate emerging therapies for brain metastases that are still in the investigational stage. Most of these therapies are available only as part of clinical trials, although "off-label" use is an option for treatment. All literature published since the original guideline, the Evidence-Based Clinical Practice Parameter Guidelines for the Treatment of Patients with Metastatic Brain Tumor,[1] published in 2010 through December 2015, was reviewed. Updates were made to prior recommendations and new recommendations addressing agents not previously were reported in the literature. For each agent, recommendations were developed based on the quality of evidence in the literature as it pertains to outcome measures, such as overall survival (OS), progression-free survival (PFS), and local response. The agents discussed in detail in this manuscript were those for which sufficient evidence was found to merit discussion. There was insufficient evidence to support formal recommendations for or against the use of most emerging treatment strategies reviewed. For these agents, the final statement included the wording "insufficient evidence to make a recommendation." For some

agents, sufficient evidence existed to make a recommendation in which case statements included the wording “level I, II, or III recommendation supporting or not supporting” the use of that agent. For each of these agents, the evidence in the literature is used to formulate the recommendation level.

METHODS

Search Strategy

Electronic databases including MEDLINE and Cochrane were searched from September 2008 (the end date of previous search) through December 2015 (the uniform cutoff established for the current guidelines series). The search strategy used combinations of sub-headings and key words and is documented in previous methodology papers. Search strategies for the root brain metastasis search as well as the 6 categories of emerging therapy can be found in Appendix A. Manuscripts selected for review upon screening of abstracts met the criteria described below.

Eligibility Criteria

Clinical studies included in the creation of guidelines addressing the questions in this manuscript were required to meet the following criteria:

- Published in English
- Involves human patients with brain metastases
- Fully published primary study published between September 2008 and December 2015
- Paper evaluates one or more of the therapies in question:
    - High-intensity focused ultrasound (HIFU)
    - Laser interstitial thermal therapy (LITT)
    - Radiation sensitizers
        - Motexafin-gadolinium
        - Temozolomide
        - Chloroquine
        - Sodium nitrite
        - Patupilone
        - Vorinostat
        - Sanazole

- Local therapy – agents or devices placed surgically at the time of tumor resection or biopsy
    - Local radiation: Intraoperative RT, I-125 seeds, cesium-131 beads
    - Local chemotherapy: carmustine wafer
- Immune modulators
    - Ipilimumab
    - Nivolumab
    - Vaccine
- Molecular targeted agents
    - HER2: trastuzumab, T-DM1, lapatinib, afatinib
    - VEGF: bevacizumab, sunitinib
    - EGFR: gefitinib, erlotinib
    - BRAF: dabrafenib, vemurafenib
    - Other: iniparib

- Number of patients with brain metastases in the study at least 5 per study arm for at least 2 of the study arms for comparative studies, and at least 5 total patients if a non-comparative study.

Data Collection Process

Manuscripts selected for review were sub-classified based on which question was addressed. Full review of each manuscript confirmed that it met eligibility criteria, or the manuscript was rejected. Data gleaned from the manuscript included type of study (eg, phase 2 clinical trial, retrospective chart review, etc.), therapeutic agent evaluated, and the outcome measures and results yielded by the study. Critical analysis of the data determined the class of evidence supported by the paper. The pertinent data and recommendation levels for each paper were entered into an evidence table for each emerging therapy subtopic. The evidence tables were then validated among the writing group prior to determining the final evidence class for each agent within each question.

Assessment for Risk of Bias

Each manuscript was evaluated by the writing group for bias, and the summation of different forms of bias are reflected in the classification system. Inherent to emerging therapy agents, initial reports were noted to be in the form of small case series, anecdotal reports, and early

phase clinical trials. As such, there is inevitable selection bias imposed by retrospective reviews and prospective studies with small numbers of patients. For example, patients selected for study, especially early phase trials, may be in better medical shape relative to patients not selected for study. Additionally, small series of patients may have bias due to random variability. Our expectation is that some of the more promising agents reviewed in this manuscript will fully 'emerge' into viable therapeutic options and be studied further as part of larger clinical trials, which will eliminate some of the inherent bias of smaller, retrospective studies.

Description of Data Classification System and Recommendation Formulation

Each manuscript that met eligibility criteria and was found to have data relevant to the question was defined as Class I, II, or III evidence based on the quality and strength of the recommendations according to the American Association of Neurological Surgeons/Congress of Neurological Surgeons (AANS/CNS) criteria. The summation of this classification system for each agent reviewed was then synthesized into a recommendation Level I, II, or III, which, for each paper, was based on classification of evidence on therapeutic effectiveness. An expanded description of the data classification system and recommendation level designation is provided in the introduction and methodology paper. Additional information and background of this process can be obtained at https://www.cns.org/guidelines/guideline-procedures-policies/guideline-development-methodology.

RESULTS

Overall Search Results

Since the Evidence-Based Clinical Practice Parameter Guidelines for the Treatment of Patients with Metastatic Brain Tumor were published in 2010, a number of emerging therapies for brain metastases were made available in clinical practice. Overall, 74 new studies (Figure 1) met eligibility criteria. A summary of the class of evidence provided by each paper is presented in Table 1.

As a group, molecular targeted agents yielded the greatest number of publications with unique clinical data, followed by immune modulators (Figure 1; Table 1). The largest and most well-designed studies include these newer agents. Surgical strategies, such as LITT and HIFU remain in the early stages of investigation in terms of clinical efficacy, and the representative studies are

smaller. Emerging therapies, such as local therapies and radiation sensitizers, were updated with clinical data published since the Evidence-Based Clinical Practice Parameter Guidelines for the Treatment of Patients with Metastatic Brain Tumor were published in 2010.

High Intensity Focused Ultrasound (HIFU)

No articles regarding the use of HIFU met criteria for inclusion in this review.

Laser Interstitial Thermal Therapy (LITT)

Study Selection and Characteristics

Among 5 manuscripts screened,[2-6] 4 met the criteria for inclusion in the guidelines (Table 2). All studies were case series without control patients in a small number of patients. The largest study described 15 patients who received LITT for previously treated brain metastases (BMs) with post-radiosurgery progression or radiation necrosis.[5] Laser interstitial thermal therapy is a minimally invasive surgical procedure in which a laser applicator is placed stereotactically and used to perform thermal ablation under magnetic resonance imaging (MRI) guidance. The other 3 studies described <10 patients each.

Results of Individual Studies

Each study demonstrated limitations inherent in small case series without a control population. Three studies used prospective data collection. In each study, LITT was demonstrated to be safe and well-tolerated. Efficacy was assessed using MRI to evaluate for local control and analysis of overall survival. Three of the studies addressed brain metastases only, while 1 included patients with other pathologies, such as glioma.[3] In the largest case series, 15 patients were followed prospectively after receiving LITT for progressive BM or radiation necrosis after prior radiation treatment for BM. At a median 24 weeks follow-up, 13 of 15 patients demonstrated local control, and the median PFS was 37 weeks.[5] The remaining 3 manuscripts described 18 patients total with BM treated with LITT. Another prospective trial evaluated 17 patients, 5 of whom had progressive BM after prior radiation. The median PFS among these 5 patients was 5.8 months.[3] The third prospective study was a pilot trial in which 7 patients with 15 BM refractory to chemotherapy and radiation were treated with LITT. In this study, local control was noted for all treated lesions at up to 30 months of follow-up, and median OS was 19.8 months.[2]

Synthesis of Results

In multiple small case series, LITT appears to be a safe treatment option for patients with BM. For patients with progressive disease after prior radiation, LITT may have value as a treatment

option. In each study reviewed, the authors acknowledged the emerging nature of LITT as a treatment option for BM and suggested that larger clinical studies were necessary to determine its efficacy.

Radiation Sensitizers

Study Selection and Characteristics

Among 11 articles that were screened at full-text, 10 met the criteria for inclusion in the evidence table (Table 3).[7-16] These manuscripts include studies published after the emerging therapy guidelines were published.[1] Two more recent manuscripts regarding motexafin gadolinium were reviewed[7, 9] and the recommendations in this guideline reflect a synthesis of this data incorporated from the 3 manuscripts reviewed in the prior guidelines paper.[7, 17, 18] Other radiation sensitizers evaluated included sodium nitrite,[16] temozolomide,[15] chloroquine, vorinostat, sanazole and patupilone. No studies were found regarding efaproxiral.

Results of Individual Studies

The 10 articles that met criteria for inclusion evaluated 7 different agents. For discussion purposes, studies are grouped based on the agent being investigated.

Temozolomide was evaluated as part of a phase 1 trial[10] in 26 patients with 49 total BM, all of which were progressive after prior radiotherapy (RT). In this prospective single-center trial with no controls, 3 sequential cohorts of patients received escalating doses of temozolomide administered prior to treating the BMs with stereotactic radiosurgery (SRS). The median PFS was 3.3 months and the median OS was 10.2 months. In a multicenter phase 2 trial, 100 patients with BM due to breast cancer were randomized to receive whole brain radiation therapy (WBRT) alone (n= 50) or WBRT plus concurrent temozolomide (75 mg/m^2/day).[15] Endpoints including median OS and median PFS were not significantly different, and the authors concluded that temozolomide did not improve local control or survival over WBRT alone in patients with BMs due to breast cancer.

Two manuscripts regarding the use of motexafin gadolinium as a radiation sensitizer met the criteria for inclusion. A multi-center phase 2 trial evaluated 65 patients who received motexafin gadolinium plus WBRT followed by SRS boost to treat up to 6 BM.[9] Motexafin gadolinium was administered with each WBRT fraction starting with fraction 6, as well as on the day of SRS

boost. In this prospective case series with no controls, the median PFS was 8 months, and the median OS was 9 months. A larger phase 3 multicenter trial randomized patients with non-small cell lung cancer (NSCLC) to WBRT alone (n= 275) or WBRT plus motexafin gadolinium (n=279).[7] Patients received the agent prior to each radiation dose. In this international study, North American patients demonstrated a median PFS of 11.8 months with WBRT alone versus 15.4 months with WBRT plus motexafin gadolinium. Overall survival was not significantly different.

A phase 1 study evaluated patupilone as a radiation sensitizer with WBRT for multiple intracranial pathologies.[8] Among 17 patients with BM, the median PFS was 19.2 months and the median OS was 23.7 months. In this study, the maximum tolerated dose (MTD) of patupilone was determined and the authors plan to conduct a phase 2 trial. Another phase 1 trial evaluated the safety of vorinostat plus WBRT in 17 patients with BM.[14] The median OS was 36 weeks, and the authors plan to use the MTD in a phase 2 trial. A feasibility study described sanazole as a radiation sensitizer for patients receiving hypofractionated SRS for recurrent BM after prior radiation therapy.[13] Median OS was 5 months.

The final 3 studies described results for sodium nitrite and chloroquine as radiation sensitizers. A phase 2 study randomized 73 patients to receive WBRT plus chloroquine (n= 39) or placebo (n= 34) for treatment of BM.[12] Although the addition of chloroquine improved local control, there was no effect on radiographic response or overall survival, and the investigators suggested further work in a phase 3 trial. In a different study, 16 patients with BM who had not had prior RT were treated with short course chloroquine and WBRT.[19] All 16 patients had either complete or partial response or stable disease. Median OS was 5.7 months. Another prospective trial randomized patients to receive WBRT with or without concomitant sodium nitrite.[16] Twenty patients were randomized, and the authors concluded that sodium nitrite did not improve radiographic response rate compared to WBRT alone.

Synthesis of Results

A significant challenge in evaluating data presented for radiation sensitizers is distinguishing the effects of radiation alone from potential added effects from the radiation sensitizer in studies without control patients. Small case series may be a valuable starting point for research into

radiation sensitizers, but larger studies are key to determining which agents may provide clinical benefit.

Building on prior data presented in the 2010 guideline on the role of emerging and investigational therapies for metastatic brain tumors,[1] more recently published evidence suggests that motexafin gadolinium may have a role as a radiation sensitizer in patients with BM due to NSCLC. In the largest study among the radiation sensitizer group, a subset of patients demonstrated statistically significant improvement in PFS. Although other agents appear safe, there does not appear to be evidence supporting the role of temozolomide as a radiation sensitizer for treatment of BM at this time. For agents such as sodium nitrite, chloroquine, patupilone, vorinostat and sanazole, there is insufficient evidence to make a recommendation given the low number of studies available for review. Among these agents, chloroquine, patupilone, and vorinostat appear to have sufficient evidence to support additional, larger clinical trials.

Interstitial Therapy

Study Selection and Characteristics

Among the 9 interstitial therapy (ie local therapy) articles that met criteria for inclusion, there were 5 brachytherapy studies, 2 carmustine wafer studies, and 1 each regarding intraoperative radiation therapy and photodynamic therapy (PDT) (Table 4). The brachytherapy, local chemotherapy, and intraoperative radiation therapy studies built on previous studies (included in the 2010 guideline on the role of emerging and investigational therapies for metastatic brain tumors), while PDT was not previously included. For discussion purposes, studies are grouped based on the agent being investigated.

Results of Individual Studies

Five studies published since 2010 regarding brachytherapy met the inclusion criteria. A single-center phase 1/2 trial evaluated 24 patients who underwent surgery plus implantation of permanent cesium-131 beads for newly diagnosed dominant BM.[20] In this prospective series without control patients, 1-year local control was 100% and the treatment regimen was safe. The other 4 brachytherapy studies reviewed involved I-125 seeds implanted surgically. In the study by Ruge et al, [21] I-125 seeds were implanted at the time of stereotactic biopsy of recurrent BM after prior SRS. Twenty-seven patients considered not candidates for surgical resection received

I-125 seeds after intraoperative confirmation of recurrent tumor as salvage therapy. One-year local control was 93.3%, and median OS was 14.8 months. The authors concluded that the treatment strategy was safe and effective as salvage therapy. A second study from the same research group compared I-125 stereotactic brachytherapy (SBT) to SRS to treat solitary BM.[22] This retrospective review evaluated 219 patients with surgically unresectable BMs. Seventy-seven of these patients underwent SBT due to factors such as tumors >14 mL, local recurrence after SRS, or if tissue was needed for histologic diagnosis. There were no differences in outcome measures, such as OS or local control, and the authors concluded that SBT is comparable to SRS for solitary BM. A third study from the same research group retrospectively reviewed 90 patients who underwent SBT for solitary BM.[23] Median survival was 8.5 months, and 1-year PFS was 94.6%. The final I-125 study evaluated 40 patients who underwent surgical resection of a dominant BM followed by permanent implantation of I-125 seeds in the walls of the resection cavity with SRS for other lesions and without adjuvant WBRT.[24] This study demonstrated similar 1-year PFS (88%) compared to other studies, and median OS was 11.3 months. The last brachytherapy study evaluated cesium-131 permanent implants placed at the time of surgical resection of brain metastasis. In this phase 1/2 trial, 24 patients with newly diagnosed brain metastasis underwent surgical resection followed by permanent implantation of cesium-131 beads. One-year local control was 100%, and median OS was 9.9 months.

Two new studies regarding carmustine wafers that met inclusion criteria were published since the 2010 guideline on the role of emerging and investigational therapies for metastatic brain tumors. One study was a retrospective case series evaluating surgery plus carmustine wafer in patients with radiographic progression of a BM following prior SRS.[25] At 6 months, PFS was 87%, and OS was 63%. Toxicities included hydrocephalus (n= 3), cerebrospinal fluid leak, and infection. The authors concluded that the treatment strategy was an effective salvage therapy for this patient population. A phase 2 trial described surgery plus carmustine wafer placement for BM, with deferral of WBRT.[26] Fifty-nine patients underwent surgery for a dominant (maximum 3 total lesions) or solitary BM with placement of carmustine wafer during surgery. Patients with multiple lesions received SRS to the other lesions. Local control was 78% at 1 year, which the authors described as comparable to historical control of surgery plus WBRT and better than WBRT alone as historical control.

A prospective study evaluated 23 patients who underwent surgical resection of a newly diagnosed solitary BM followed by intraoperative radiation therapy in the operating room using a portable radiation device.[27] The tumor cavity was measured intraoperatively to plan radiation, and 14 Gy was delivered to a depth of 2mm. Mean PFS was 22 months with 5-year follow-up, and the authors concluded the treatment strategy was safe with local control rates comparable to other adjuvant radiation techniques.

Photodynamic therapy (PDT) was evaluated in 14 patients who underwent surgery for resection of BM.[28] In this case series, PDT was used intraoperatively after removal of the brain metastasis. Among the 14 patients, 2 died of progressive brain metastasis, and 7 died of systemic disease.

Synthesis of Results

The term 'interstitial therapy' or 'local therapy' has diverse meanings. Well-known strategies, such as brachytherapy and carmustine wafers, demonstrate safety and outcomes comparable to more established strategies, such as SRS for the treatment of BM. Stereotactic brachytherapy may represent a reasonable option for unresectable tumors or as salvage therapy. Although it is a retrospective review, the study comparing SBT to SRS involved a large number of patients, and the SBT group was generally at a disadvantage in terms of prognosis due to the inclusion of previously treated BM. Although SBT is a surgical procedure, it is minimally invasive, and therefore, it is available for patients who are not amenable to aggressive surgical management. Additionally, techniques such as carmustine wafers and SBT do not preclude additional radiation therapy.

In the 2010 guideline on the role of emerging and investigational therapies for metastatic brain tumors, 7 clinical studies were discussed regarding brachytherapy, 2 studies presented data regarding local chemotherapy, and 2 presented interstitial radiosurgery clinical studies. All studies provided Class III evidence except for 1 retrospective cohort study regarding temporary I-125 seeds. All 8 studies reviewed for this guideline are Class III evidence. As expected, when evaluated as a group, no recommendations can be made regarding the use of any of the strategies in this category for patients with BM. There may be a role for these emerging therapies as salvage therapy for BM that progress despite prior treatment. However, larger studies are

necessary to validate their efficacy. Other local techniques, such as convection enhanced delivery, do not appear to be under investigation for the treatment of BM.

Immune Modulators

Study Selection and Characteristics

Among 24 screened manuscripts, 10 studies met inclusion criteria for final analysis in the immune therapy sub-question (Table 5). Common reasons for exclusion were the inability to parse out data specific to BM or a lack of baseline data from which a conclusion could be accurately made. Among the 10 included studies, 7 focused on ipilimumab, 2 on adoptive cell transfer, and 1 on melanoma antigen vaccine. For discussion purposes, studies are grouped based on the agent being investigated. Unlike other emerging therapies for BM, literature searches for immune modulators like ipilimumab or molecular targeted agents (see molecular targeted section) identified a larger number of studies, but a smaller percentage of these studies focused specifically on BM. This increased the difficulty in extracting data specific to BM and led to a higher rate of exclusion of clinical studies among these 2 sub-sections.

Results of Individual Studies

The 7 studies involving ipilimumab involved a combined 321 patients, all with metastatic melanoma BM. The largest in terms of patients was an expanded access program in Italy, which provided compassionate use ipilimumab for patients with metastatic melanoma who did not qualify for a clinical trial.[29] Among 855 patients in the study, 146 had asymptomatic BM at the time of study entry. Retrospective analysis of these patients revealed 4 complete responses, 13 partial responses, and 22 patients with stable disease with a median 9.7 months duration of response. The median PFS was 2.8 months and the median OS was 4.3 months. The other 6 studies involved 12 to 72 patients. Four retrospective studies incorporating 83 patients contribute to the evidence that ipilimumab is safe but did not provide convincing evidence of efficacy.[30-33] Two prospective phase 2 trials concluded that ipilimumab had some clinical activity in patients with melanoma BM. One multicenter study used ipilimumab plus fotemustine to treat metastatic melanoma.[34] Twenty of 86 enrolled patients had asymptomatic BM due to melanoma. With the treatment regimen, 10 of these 20 patients had disease control, although 55% had a treatment-related adverse event. The other phase 2 trial evaluated 72 patients with melanoma BM in 2 cohorts.[35] Cohort A (n= 51) were asymptomatic at presentation, and cohort B (n= 21) were neurologically symptomatic on stable steroid doses. After 12 weeks of ipilimumab therapy, 24%

of patients in cohort A and 10% of patients in cohort B had disease control of their BM, suggesting to the authors some activity of ipilimumab.

Adoptive cell transfer with autologous antitumor lymphocytes plus interleukin-2 was used to treat 264 patients with melanoma in a prospective trial.[36] A subset (n= 26) of these patients with BM were retrospectively analyzed for response of the BM to treatment. The data presented are difficult to fully interpret due to differences in other treatment strategies (radiation) and doses of other therapeutic agents, such as interleukin-2. However, complete and durable responses of BM in some patients was noted, and additional studies are planned by the investigators. Adoptive immunotherapy was investigated as part of a retrospective case control study involving 108 patients with metastatic NSCLC.[37] In this study, 54 patients received adoptive immunotherapy (no surgery, chemotherapy, or radiation), and 54 patients received standard of care (surgery, chemotherapy, and/or radiation). Fourteen patients in the experimental arm and 13 in the standard of care arm had BM. Among the BM patients, median OS was 19.6 months in the immunotherapy cohort and 22.7 months in the control cohort.

A prospective single-center study evaluated the use of melanoma antigen vaccines in 22 patients with metastatic melanoma, of whom 8 had previously treated BM.[38] Although there were no treatment-related toxicities, 7 of the 8 patients with BM demonstrated radiographic progression during the 90-day follow-up period.

Synthesis of Results

Among the 12 articles included in the final analysis, none provided Class I or II evidence. Ipilimumab appears safe, and Class III evidence supports possible activity in patients with BM due to metastatic melanoma; however, larger studies are needed. Other therapies studied, including adoptive cell transfer and melanoma antigen vaccine, have insufficient evidence to make a recommendation. No articles regarding nivolumab met criteria for inclusion.

A topic somewhat unique to newer agents, such as immune modulators and molecular targeted agents, is the question of how to determine specific response of BM. The notion of ‘treatment effect’ or ‘pseudo-progression’ may have relevance in patients receiving these treatments because the radiographic response of BM to these agents has not been fully elucidated. Put

another way, interval increase in enhancement may represent treatment failure, or it may represent an exaggerated inflammatory or immune response with increased permeability of the blood-brain barrier.

Molecular Targeted Therapy

Study Selection and Characteristics

Among 67 manuscripts screened, 41 were included in the final analysis (Table 6). Since the 2010 guideline on the role of emerging and investigational therapies for metastatic brain tumors, a large number of studies regarding molecular targeted agents have been published. However, as mentioned in the immune modulator section, studies regarding molecular targeted agents for the treatment of metastatic cancer often incorporate data for patients with BM, even if the treatment of BM is not the specific focus of the study. Data regarding patients with BM are sometimes mentioned specifically and evaluable for this guidelines paper. However, nearly 20 studies were excluded because BM data could not be extracted or were incompletely included in the article. In this section, only articles for which BM-specific data are available are included.

These 41 studies can generally be divided by the type of cancer chosen for treatment. For example, EGFR inhibitors, including gefitinib and erlotinib, generally target a subset of patients with NSCLC. Similarly, BRAF V600E inhibitors are generally used to treat melanoma. For discussion purposes, studies are grouped based on the specific primary cancer associated with brain metastasis as well as the specific agent being investigated.

Results of Individual Studies

Among the 41 studies included in the final analysis, 14 involved anti-HER2 agents for breast cancer BM (afatinib, lapatinib, trastuzumab and TDM-1), 12 involved EGFR inhibitors (gefitinib and/or erlotinib), 8 involved BRAF V600E inhibitors (dabrafenib or vemurafenib), and 6 involved anti-VEGF agents (bevacizumab or sunitinib). Iniparib, previously thought to be a poly ADP ribose polymerase inhibitor, is no longer in testing, but is included here in the breast cancer section for completeness of results.

Breast Cancer

Among 14 studies that focused on an anti-HER2 agent, 10 evaluated lapatinib, 2 trastuzumab, and 1 each for afatinib and TDM-1. A single study focused on iniparib, a now defunct agent.

Lapatinib is an anti-HER2 agent studied as a treatment for breast cancer and is the most represented agent in the emerging therapy for BM guidelines, although no studies have been published since 2013. The types of studies vary from larger multicenter trials to small, single center studies focused on specific clinical presentations. Use of lapatinib with radiation is the focus of 2 studies. A retrospective single center study evaluated 80 patients with 707 breast cancer BM who underwent SRS.[39] Forty of these patients had HER2+ breast cancer, and 24 of these 40 patients received lapatinib-based therapy. Lapatinib-based therapy was associated with improved local control (86% versus 69%) compared to the 16 patients who received non-lapatinib-based therapy, demonstrating safety and possible efficacy of this treatment regimen. A phase 1 study was conducted to determine the MTD of lapatinib when given concomitantly with WBRT for HER2+ breast cancer BM.[40] This multi-center trial enrolled 35 patients, and 6-month PFS was 46%, although conclusions regarding lapatinib activity are difficult without a control population.

Lapatinib as part of the systemic treatment regimen is the focus of multiple studies, some of which have data regarding patients with BM. In one retrospective study, 201 patients with progressive, metastatic breast cancer are evaluated, 11 of whom have BM.[41] Among the BM subset of patients, adding lapatinib improved OS and use of trastuzumab showed a trend towards a decrease in developing BM during therapy. Each group was compared to a control cohort of patients who were treated prior to the routine use of trastuzumab. Another study evaluated 356 patients previously treated with trastuzumab, anthracycline and taxane as part of an expanded access program using lapatinib to treat HER2+ breast cancer.[42] Of the 356 patients, 34 had BM and were retrospectively analyzed. Response rate was 21% and PFS 22 weeks, which the authors felt to compare favorably in a patient population heavily treated.

Some studies focused solely on systemic therapy for breast cancer BM. Early work showed that patients with HER2+ breast cancer BM treated with lapatinib plus capecitabine demonstrated significantly improved overall survival compared to patients treated with trastuzumab alone, and that activity against BM could be demonstrated radiographically either as partial responses or stable disease.[43] A retrospective study evaluated the impact of trastuzumab and lapatinib versus HER2+ breast cancer BM.[44] Among 80 patients with BM, 43 received trastuzumab, and 37

patients treated prior to 2003 when the standard recommendation was to discontinue trastuzumab use upon diagnosis of BM served as a control group. Fifteen of these 43 patients also received lapatinib, and these patients demonstrated increased OS compared to trastuzumab alone. Other work regarding lapatinib for HER2+ breast cancer BM involves formal clinical trials. Two early phase 2 trials evaluated lapatinib alone for HER2+ breast cancer BM.[45, 46] Neither study had a control group, and both found modest activity of lapatinib monotherapy in this patient population, but improved CNS response rate when lapatinib was given in combination with capecitabine. Subsequently, a phase 2 multi-institution trial evaluated lapatinib plus capecitabine for previously untreated HER2+ breast cancer BM.[47] Of the 44 patients treated, 29 had greater than 50% reduction in CNS BM volume, though there were no complete responses. The authors concluded this regimen has activity versus BM and should be investigated further in phase 3 trials. Another phase 2 trial compared lapatinib plus capecitabine to lapatinib plus topotecan for HER2+ breast cancer BM.[48] Only 22 of 110 patients were enrolled and randomized due to toxicity and lack of efficacy in the topotecan arm (no response) compared to the lapatinib plus capecitabine arm (38% BM response rate). Again, parsing out the exact contribution of the molecular targeted agent of interest (lapatinib) is difficult, but the lack of activity in the lapatinib plus topotecan arm is potentially concerning when trying to attribute CNS effects to lapatinib.

Trastuzumab plus WBRT was evaluated for efficacy in treating HER2+ breast cancer BM in 31 patients in a single center retrospective study.[49] Median OS was 18 months and median brain PFS was 10.5 months. Twenty-three patients had either complete response or partial response. As with similar studies in which an agent is given concomitantly with radiation, the true effects of the agent on BM are unclear, although the treatment strategy appears to be safe. Another study retrospectively analyzed 94 patients with BM due to breast cancer.[50] The results showed trastuzumab use was associated with longer OS, although the authors felt this was likely due to improved systemic disease control. A phase 2 multicenter study evaluated 121 patients with HER2+ breast cancer with BM.[51] Patients received afatinib with vinorelbine (38), afatinib alone (40) or investigator choice therapy (43). In this randomized prospective trial, afatinib was associated with a higher rate of toxicity and no improvement in outcomes. The authors recommended no further study of afatinib in this patient population. Another anti-HER2 agent, T-DM1, is an antibody drug conjugate linking trastuzumab to a cytotoxic anti-microtubule agent

(DM1). A recent case series described 10 patients with breast cancer BM treated with T-DM1.[52] Five patients had partial response or stable disease and intracranial PFS was 5 months. The authors felt the results did not improve upon the standard option (lapatinib plus cytarabine) for local therapy failure.

Completing the breast cancer section is a multicenter phase 2 trial of iniparib plus irinotecan to treat progressive triple negative breast cancer BM.[53] Thirty-seven total patients were enrolled in either cohort 1 (progressive BM after radiation) or cohort 2 (newly diagnosed BM). Median PFS was 2.1 months, median OS was 7.8 months, and the intracranial response rate was 12%. Interpretation of these results is hindered by the co-administration of irinotecan, but the authors concluded there was modest activity of this regimen for BM in this patient population. The proposed mechanism of action of iniparib has since been disproven, and this agent is no longer in trials.

NSCLC

Studies that involved patients with NSCLC BM largely fell into two categories: EGFR inhibitors and VEGF inhibitors. Results from the analysis of the manuscripts are presented separately here.

EGFR Inhibitor

Twelve studies focused on EGFR inhibitors, 3 gefitinib, 8 erlotinib, and 1 both. Studies that did not distinguish between the two agents were excluded from analysis, although some are mentioned in the subsequent discussion. Many studies focused on EGFR-mutant NSCLC, although recent work has shown the benefits of EGFR inhibitors in patients without EGFR mutation.

A phase 1 study evaluated the safety of erlotinib plus WBRT to treat multiple NSCLC BM.[54] Eleven patients in 2 different dose cohorts were studied, and two patients in the high dose group died due to interstitial lung disease related to erlotinib. Among 7 evaluable patients, 5 had partial response and two had stable disease at three months. Other small case series similarly showed possible activity of erlotinib in patients with NSCLC BM, and possibly more activity in patients with EGFR-mutant NSCLC.[55-57] Similar small case series evaluating gefitinib also demonstrated acceptable safety and possible activity in patients with NSCLC BM. In a randomized prospective trial, 73 patients with multiple NSCLC brain metastases were randomized to receive

WBRT plus either gefitinib alone or VM-26 and cisplatin.[58] Response rates were similar among the two groups and there were no differences in response within the gefinitib group based on EGFR status. Toxicity was lower among the gefitinib group. One study compared erlotinib to gefitinib and found no statistically significant differences in PFS and OS in patients with EGFR-mutant NSCLC BM.[59] Another study used gefitinib as first line therapy without radiation in patients with newly diagnosed EGFR-mutant NSCLC BM.[60] Forty-one patients were enrolled and received gefitinib until disease progression, erlotinib at progression and WBRT as salvage after progression on erlotinib. Response rate was 88% and median PFS was 14.5 months. Exon 19 deletion EGFR mutation patients were noted to respond most favorably. Another phase 2 trial evaluated erlotinib plus WBRT for NSCLC BM.[61] This study enrolled 40 patients and had no control population. CNS response was 86%, and median OS was 11.8 months (9.3 months for EGFR wt and 19.1 months for EGFR-mutant).

A randomized phase 2 trial compared patients with NSCLC BM treated with WBRT plus gefitinib or WBRT plus temozolomide.[62] Fifty-nine patients with multiple NSCLC BM were enrolled, and 16 received gefitinib. Median PFS was worse in the gefitinib group, although median OS was longer. The authors concluded that both treatment regimens were unsatisfactory and that their data do not support using either regimen.

A non-randomized trial compared patients with multiple NSCLC BM who received WBRT alone (31) to those who received WBRT plus erlotinib (23).[63] The response rate was 55% in the WBRT group and 96% in the WBRT plus erlotinib group, and there were no differences in response based on EGFR mutation status. Median PFS and OS were improved in the erlotinib group also, and the authors stated that the data supported activity of erlotinib versus BM in NSCLC. However, in a phase 3 trial, 126 patients with 1 to 3 BM were randomized to three treatment arms: WBRT plus SRS, WBRT plus SRS plus temozolomide, or WBRT plus SRS plus erlotinib.[64] In this study, neither temozolomide nor erlotinib improved OS or PFS compared to WBRT/SRS alone, and toxicities and performance status were significantly worse in both the temozolomide and erlotinib groups. The authors concluded that the two agents did not improve survival but state that the study was underpowered. Another randomized controlled multicenter trial compared WBRT plus erlotinib (40) to WBRT plus placebo (40) in 80 patients with

untreated, newly diagnosed NSCLC BM.[65] Median PFS was 1.6 months in both groups. There was a low frequency of EGFR mutation, and the authors concluded there was no role for erlotinib in patients with EGFR wt NSCLC BM.

Bevacizumab

A small retrospective series evaluated 6 patients with NSCLC BM who received bevacizumab.[66] Two patients demonstrated partial radiographic response, and median PFS was 4.7 months. The authors noted improved neurologic symptoms and decrease steroid use, and determined that bevacizumab was safe and that further studies were warranted. A subsequent study evaluated bevacizumab as front-line therapy for NSCLC brain metastases that were not deemed as candidates for local therapy.[67] Among 18 patients enrolled, most had NSCLC BM that were treatment naïve. All demonstrated either partial response or stable disease on serial MRI. Median PFS was 14 months, and the authors concluded there was possible activity. Subsequent studies regarding bevacizumab for BM have involved similar small numbers of patients followed prospectively but without a control group, and each has showed safety with possible activity.[68-70] The largest of these was a phase 2 trial evaluating bevacizumab for treatment of asymptomatic, newly diagnosed NSCLC BM.[70] Sixty-seven patients received bevacizumab plus carboplatin and paclitaxel, and 24 patients received bevacizumab plus erlotinib. Median PFS was similar between the two groups, and the authors concluded the treatment regimen was safe with some activity.

Melanoma

Use of BRAF V600E inhibitors to treat melanoma BM was the subject of 8 studies that met inclusion criteria. Of these, 5 were studies regarding vemurafenib, and 3 were regarding dabrafenib.

A phase 1 trial evaluated the safety and MTD of dabrafenib in cancers including melanoma.[71] Among the 10 patients with melanoma included in the trial, 9 demonstrated observable radiographic response, and median PFS was 4.2 months. A subsequent phase 2 trial enrolled 172 patients with at least one asymptomatic BM with the goal of determining intracranial response to dabrafenib.[72] Eighty-nine patients had no prior local therapy, and 83 had progressive BM after local therapy. Among patients evaluable for response, 29 of 74 patients with no prior therapy demonstrated intracranial response and 20 of 65 progressive BM demonstrated response,

implying activity of dabrafenib. Other case series have shown that intracranial and extracranial disease responds similarly to dabrafenib.[73]

Similar small case series regarding vemurafenib for treatment of V600-mutant melanoma BM have shown safety and are suggestive of activity against BM, possibly improved compared to dabrafenib.[74-76] Vemurafenib was shown to be safe when administered concurrently with SRS in a small case series.[77] The largest case series retrospectively evaluated 27 patients with BRAF-mutant melanoma treated with vemurafenib.[78] Intracranial response rate was 50%, and median intracranial PFS was 4.6 months.

Renal Cell Carcinoma (RCC)

The only study to evaluate sunitinib was a retrospective review of 6 patients with BM due to renal cell carcinoma who had not received prior surgery or radiation.[79] Two patients demonstrated a complete CNS response that was durable for 23 and 47 months.

Synthesis of Results

Patients with metastatic cancer are increasingly being treated with molecular targeted agents, either as part of first-line therapy or as second-line therapy, once standard chemotherapeutic regimens have failed. Anti-HER2 molecular agents are widely used to treat metastatic breast cancer, and 15 studies over the past 5 years have provided data regarding breast cancer BM. Evaluation of BM data is often complicated by the concomitant use of chemotherapy agents, simultaneous use of multiple molecular targeted agents, or differences among study patients in terms of prior systemic therapy. This is especially true for patients with breast cancer BM, and many of the studies discussed above involved the use of an anti-HER2 agent in patients who had already received systemic therapy with a molecular targeted agent prior to enrollment in the study. This prevents clarity regarding the activity of specific molecular agents against breast cancer BM because the effects of the agent cannot be isolated or compared to a control group. Currently, a common regimen is lapatinib plus capecitabine, although the contribution of lapatinib versus BM is uncertain, as discussed above.

Class III evidence supported the safety of EGFR TKI in NSCLC BM patients, and suggested potential efficacy. In addition to the studies discussed above and presented in Table 5, other studies contributed evidence towards this conclusion, but could not be incorporated into the data

in this guideline paper due to not meeting inclusion criteria. These studies evaluated both erlotinib and gefitinib without separating data based on the 2 different molecular targeted agents.[80-83] Although Class III data supported the concept of safety and efficacy of EGFR TKI in patients with NSCLC BM, subsequent larger, prospective trials provided conflicting evidence. Class II evidence from a non-randomized controlled trial demonstrated that erlotinib added to WBRT improved outcomes for patients with NSCLC BM. However, 2 separate studies, which provided Class I and Class II evidence, indicated no role for erlotinib in NSCLC BM patients due to lack of efficacy and significant toxicity.

BRAF V600E-mutant metastatic melanoma is often treated with molecular targeted agents dabrafenib and vemurafenib. Existing studies focusing on patients with BM are small and provided only Class III evidence of safety and activity. One small retrospective study was excluded due to the data presented not distinguishing between BRAF inhibitors.[84] At this point, BRAF inhibitors need larger prospective studies to validate findings of small case series in patients with melanoma BM.

Aside from the clinical studies centered on HER2+ breast cancer, BRAF V600E-mutant melanoma, and EGFR+ NSCLC, the other molecular targeted agent studies that met criteria for inclusion are essentially small, anecdotal case series. VEGF inhibitors (eg, bevacizumab) and TKIs with VEGF inhibition as one mechanism of action (eg, sunitinib) were the topic of 5 studies included in this analysis. Of note, a significant number of clinical studies regarding molecular targeted VEGF agents were found and ultimately rejected due to the inability to extract data specific to the molecular targeted agent in question.[85-89] Each of these studies evaluated patients primarily with RCC BM.

Investigation into the molecular and genetic findings of cancer has led to potential therapeutic inroads culminating in the development of these molecular targeted agents. However, clinical work evaluating their efficacy for BM is in the early stages, and further investigation is needed to determine the therapeutic role.

DISCUSSION

Emerging therapies for brain metastases involve a number of treatment categories. Systemic therapies include categories such as molecular targeted agents, immune therapy, and radiation sensitizers. Local strategies include interstitial modalities, LITT, and HIFU.

Data available regarding LITT is solely in the form of small case series, so there is insufficient evidence to develop recommendations. A role for treatment of recurrent BM after prior radiation is suggested as safe by the available data, and is the most common clinical scenario described in the literature.[2-5] There was insufficient evidence to make a recommendation regarding HIFU as a treatment strategy for BM.

The 2010 guideline on the role of emerging and investigational therapies for metastatic brain tumors discussed radiation sensitizers and interstitial modalities. At that time, there was insufficient evidence to make recommendations supporting the use of any modality in these subgroups.[1] Data published since that guideline do not substantially add to or subtract from these recommendations.

Among radiation sensitizers, Class I evidence indicates that there does not appear to be a role for temozolomide added to WBRT in patients with breast cancer BM.[15] Class II data was published regarding the use of WBRT plus sodium nitrite in patients with BM,[16] and chloroquine plus WBRT in patients with BM.[12] The former study involved only 20 patients, whereas the latter enrolled 73 patients and used a placebo in the control group. For both studies, there was no difference in outcomes with the trial agent compared to WBRT alone. Class III evidence in this category supports the safety of agents such as patupilone,[8] vorinostat,[14] and sanazole,[13] but further clinical data is necessary prior to making a recommendation. There are no changes to prior recommendations regarding the use of motexafin gadolinium as a radiation sensitizer.[1]

No data published since the 2010 guideline on the role of emerging and investigational therapies for metastatic brain tumors provided Class I or Class II evidence for the use of interstitial therapy, also termed local therapy. A number of case series demonstrated safety and suggested potential efficacy for modalities such as carmustine wafer[25, 26] and local radiation techniques.[20-24, 27] Of the 2 studies involving carmustine wafers, a retrospective study analyzed 31 patients with

progressive BM despite prior RT. For these patients, surgery with tumor resection and wafer implantation was performed as salvage therapy. The other carmustine wafer study involved 59 patients for resection of a solitary or dominant BM with placement of carmustine wafers. In both studies, there was no control population, which makes analysis of efficacy difficult, although the treatment strategy overall seemed safe. There is also the potential for selection bias, as patients selected were thought to be surgical candidates and therefore likely in better condition than other patients not chosen for study, which makes any potential comparison to historical controls problematic.

Brachytherapy and local radiation studies included three prospective studies, but the number of patients included ranged only from 24 to 30.[20, 21, 27] The largest study in this subgroup was a retrospective review of 219 patients who underwent either SRS or surgery for stereotactic placement of I-125 seeds (SBT).[22] Patients in this study were noted to have SRS for smaller tumors and in cases where tissue was not desired, whereas the SBT group typically had larger tumors or tumors progressive after prior radiation. The authors noted no differences in outcomes between the 2 groups. Although this is Class III data, it is worth noting that patients in the SBT group may have started at a disadvantage overall due to the inclusion of SRS treatment failure patients and those with an average larger tumor burden.

The primary difficulty encountered when evaluating systemic emerging therapies is the confounding variables allowed in inclusion criteria, whereas studies regarding local therapies are less susceptible to being confounded by varied treatment strategies among patients included in analysis. In some studies, the treatment of interest is initiated with another agent. For example, in the studies reviewed regarding molecular targeted therapies for breast cancer BM, cytotoxic agents, such as irinotecan[53] and capecitabine,[41, 44] were often initiated in addition to the most commonly investigated molecular agent for breast cancer BM, lapatinib. The few studies that included an emerging therapy (lapatinib) as monotherapy showed possible modest activity,[45, 46] but when a chemotherapy agent (capecitabine) was added the effect was more pronounced.[47, 48] Another common clinical trial design was to initiate a molecular targeted agent simultaneously with radiation therapy, which renders outcomes, such as local response, difficult to interpret without large studies that include control patients. In these trials and case series, use of systemic

agents, such as molecular targeted therapy[40, 49] and immune therapy with radiation, was shown to be safe, but the true effects of the emerging therapy agent are difficult to distinguish.

A few large studies regarding molecular targeted agents had appropriate controls and randomization, but the results were largely disappointing. A randomized controlled trial investigated afatinib for treatment of breast cancer BM progressive after prior trastuzumab, lapatinib, or both.[51] The 121 eligible patients were randomized to afatinib alone, afatinib plus vinorelbine, or investigator choice. Not only was afatinib not associated with improved outcomes, but the agent was associated with significantly higher toxicity, and the authors concluded that afatinib should be abandoned as a therapeutic agent for breast cancer.

Within the time frame of the literature review, erlotinib for treatment of NSCLC BM ran the course from early case series through late phase clinical trials. Initially, the results were promising with case series showing that erlotinib is safe with possible activity in patients with NSCLC BM. In some studies, patients with EGFR mutation appeared to have a better response to erlotinib. However, among the Class I and II evidence are mixed results for erlotinib as a treatment for NSCLC BM. Class I evidence comes from a randomized trial of erlotinib plus WBRT versus placebo plus WBRT for NSCLC BM.[65] Eighty patients were randomized, and outcomes in this study were not improved with erlotinib. Most patients in this study were EGFR wt, and the authors concluded that there was no role for erlotinib in patients with NSCLC EGFR wt with BM. One phase 3 and one phase 2 study, which arrived at different conclusions regarding the value of erlotinib in patients with NSCLC BM, provided Class II evidence. The phase 3 trial of WBRT plus SRS plus erlotinib or temozolomide versus WBRT plus SRS alone for patients with 1 to 3 NSCLC BM not only showed no improvement in outcome with erlotinib, but showed higher toxicity in the erlotinib group.[64] However, the phase 2 study of WBRT plus erlotinib versus WBRT alone in patients with multiple NSCLC BM showed that erlotinib use was the most important prognostic factor for prolonged survival on multi-variate analysis.[63] Differences in the 2 studies may have contributed to the results. For example, the phase 3 trial enrolled 125 patients with 1 to 3 BM, whereas the phase 2 trial enrolled 54 patients with 2 to 12 BM. Although the phase 3 trial is larger, the authors note that it is underpowered.

Immune therapy data is only Class III. The strongest statements that can be made in this subgroup are that agents such as imilimumab and melanoma antigen vaccines appear safe and that further work is needed to elucidate a role in treating patients with BM. The clinical data reviewed was largely for patients with melanoma BM, and some manuscripts involved a review of the subset of patients with BM enrolled in larger clinical trials. For example, a large European expanded access trial enrolled 855 patients with metastatic melanoma.[29] When analyzing the data retrospectively, the authors noted 146 patients with asymptomatic BM, although a brain MRI was not required at enrollment, and some patients with BM may have been missed. Seventeen of the 145 evaluable patients demonstrated radiographic response, and 22 showed stable disease. The authors concluded there was likely some benefit for patients with BM, although acknowledging the trial was not designed for this type of analysis. An earlier phase 2 trial evaluated 72 patients with melanoma BM and divided patients into those asymptomatic at study entry (51) and symptomatic on stable steroid doses (21). This prospective trial had no control group, which limits the data to Class III. Patients with asymptomatic tumors had a higher chance of disease control (24%) at 12 weeks versus symptomatic patients (10%). The authors felt their findings suggested some activity, especially with small, asymptomatic tumors. At this point, the summation of literature regarding immune modulation for BM would be that ipilimumab is safe in this patient population, and there may be some clinical activity.

Since 2009, only 8 published articles provided evidence Class I or II data for any emerging therapy treatment modality for brain metastases. Four of these were for radiation sensitizers, and 4 were for molecular targeted agents. Of these 8 articles, 5 concluded that the emerging therapy provided no benefit for patients in terms of the outcome metric being measured. These 5 articles included 3 of the 4 studies that provided Class I evidence. Therefore, only 3 studies demonstrated a benefit of the emerging therapy agent on patient outcome. One study, the only Class I evidence of the 3, showed that chloroquine added to WBRT improved PFS, but not OS, in patients with BM. Another study provided Class II evidence that motexafin gadolinium given concurrently with WBRT may improve PFS in patients with NSCLC BM. The final study of the 3 “positive” studies provided Class II evidence in support of the use of erlotinib in patients with NSCLC BM. However, results from this final study are contradicted by 2 other studies among the 8 that provide Class I or II evidence. In these 2 studies, one providing Class I evidence and

the other Class II evidence, the authors concluded that there was no role for erlotinib in patients with NSCLC BM based on their results. Thus, the best designed studies included in this analysis generally failed to yield data in favor of an emerging therapy agent.

CONCLUSION AND KEY ISSUES FOR FUTURE INVESTIGATION

A number of emerging therapies for brain metastases hold significant therapeutic potential. Inherent to an 'emerging therapy,' however, is the general lack of existing Class I data sufficient to make a Level 1 recommendation regarding these modalities. Currently, the best data is largely negative. For example, Class I data suggests no role for afatinib to treat breast cancer BM, and no role for erlotinib to treat EGFR wt NSCLC BM. For other emerging therapy categories, the data is mostly Class II and Class III, underscoring the need for further investigation. For example, Class III data suggests a potential role for molecular targeted agents such as dabrafenib for melanoma brain metastases, and surgical strategies, such as LITT, for recurrent brain metastases.

A significant amount of new evidence, specifically regarding immune modulation and molecular targeted agents is expected to emerge in the coming years. The guidelines presented here cover the time frame through the end of 2015. The authors recognize that significant clinical trial results have been published after this 2015 cutoff and are not reviewed in this manuscript. These trials involve more recent results with immunotherapy agents such as nivolumab and pembrolizumab, as well as trials involving newer agents not mentioned in this manuscript such as alectinib and osimertinib. The near future will likely see a continued explosion of data regarding the varied new molecular and immune modulatory agents, and results from trials published after 2015 will be key components in the development of future guidelines. The key to delineating a role for each agent specific to treatment of brain metastases will be well-designed clinical trials. Similarly, the promise shown by local interventions such as LITT will only be revealed by prospective clinical trials with adequate controls. The Congress of Neurological Surgeons Guidelines Committee will continue to monitor literature regarding emerging therapies for brain metastases at least every 5 years to ensure continued validity and maintain current recommendations.

Potential Conflicts of Interest (COI)

The Brain Metastases Guideline Update Task Force members were required to report all possible conflicts of interest (COIs) prior to beginning work on the guideline, using the COI disclosure form of the AANS/CNS Joint Guidelines Review Committee, including potential COIs that are unrelated to the topic of the guideline. The CNS Guidelines Committee and Guideline Task Force Chair reviewed the disclosures and either approved or disapproved the nomination. The CNS Guidelines Committee and Guideline Task Force Chair are given latitude to approve nominations of task force members with possible conflicts and address this by restricting the writing and reviewing privileges of that person to topics unrelated to the possible COIs. The conflict of interest findings are provided in detail in the companion introduction and methods manuscript.

Disclosures

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Disclaimer of Liability

This clinical systematic review and evidence-based guideline was developed by a multidisciplinary physician volunteer task force and serves as an educational tool designed to provide an accurate review of the subject matter covered. These guidelines are disseminated with the understanding that the recommendations by the authors and consultants who have collaborated in their development are not meant to replace the individualized care and treatment advice from a patient's physician(s). If medical advice or assistance is required, the services of a competent physician should be sought. The proposals contained in these guidelines may not be suitable for use in all circumstances. The choice to implement any particular recommendation contained in these guidelines must be made by a managing physician in light of the situation in each particular patient and on the basis of existing resources.

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Figure 1 PRISMA Flow Chart

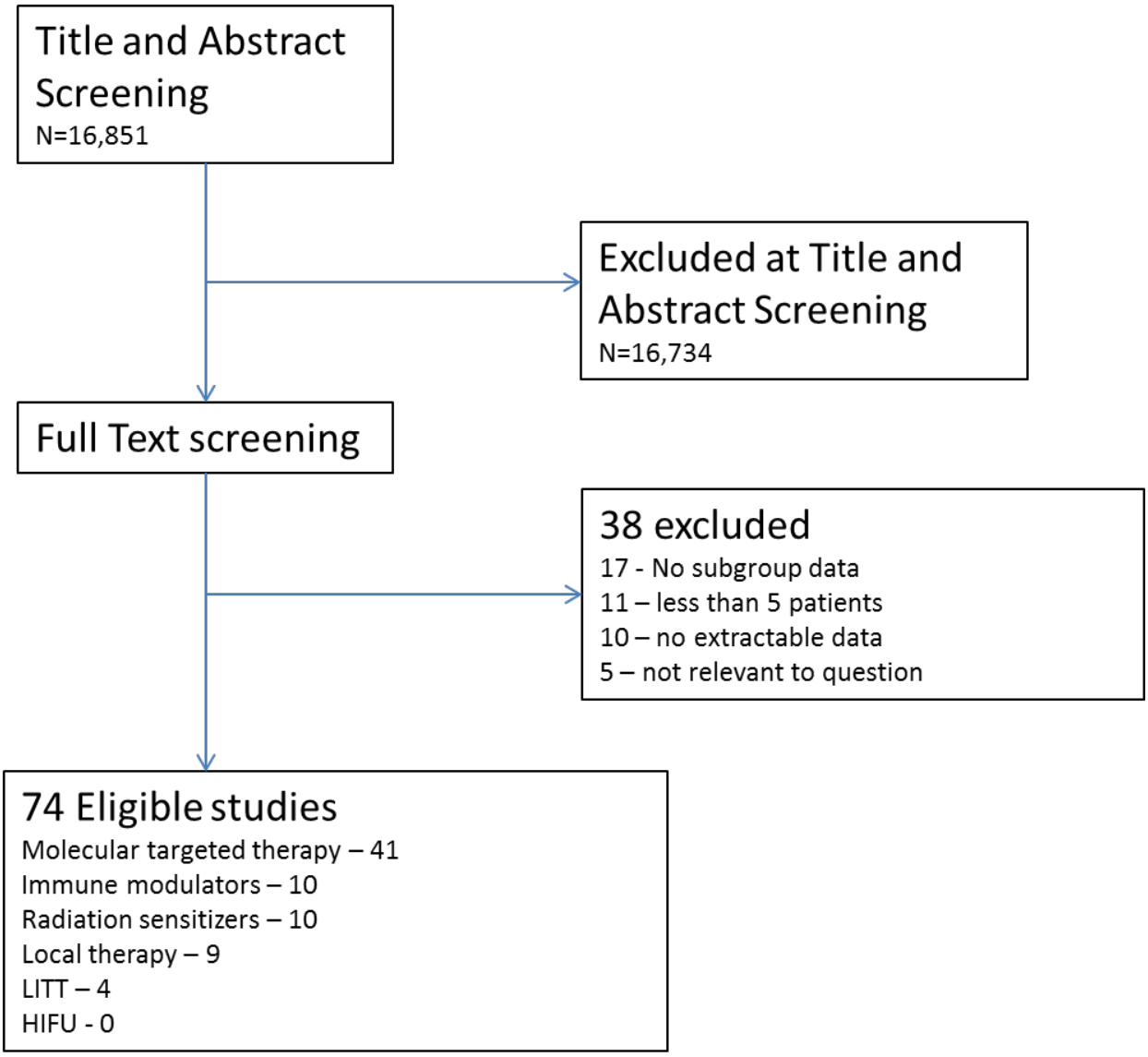

Table 1. Composite Table of Reviewed Studies Organized by Evidence Class and Category of Emerging Therapy.

Each paper is classified based on evidence of therapeutic effectiveness.

Evidence Class	Description of Evidence Class	Associated Studies
LITT		
Class I	Evidence provided by one or more well-designed clinical trials, including overview (meta-analyses) of such trials	None
Class II	Evidence provided by well-designed observational studies with concurrent controls (eg, case-control and cohort studies)	None
Class III	Evidence provided by expert opinion, case series, case reports, and studies with historical controls	3 prospective case series with no controls[2,3,5] 1 retrospective case series with no controls[4]
Radiation Sensitizers		
Class I	Evidence provided by one or more well-designed clinical trials, including overview (meta-analyses) of such trials	RCT: No role for temozolomide + WBRT in breast cancer BM[15] RCT: chloroquine added to WBRT may improve PFS but not OS in patients with BM[12]
Class II	Evidence provided by well-designed observational studies with concurrent controls (eg, case-control and cohort studies)	RCT: motexafin gadolinium given concurrently with WBRT may improve PFS in patients with BM due to NSCLC[1,7] RCT: no effect of sodium nitrite when given with WBRT[16]
Class III	Evidence provided by expert opinion, case series, case reports, and studies with historical controls	Phase 1 trial: temozolomide safe given concurrently with SRS for BM[10] Phase 2 trial: motexafin gadolinium concurrent with WBRT and SRS is safe[9] Phase 1 trial: patupilone safe and phase 2 trial planned[8]; vorinostat safe and phase 2 trial planned[14] Case series: sanazole safe[13]
Local Therapy		

Evidence Class	Description of Evidence Class	Associated Studies
Class I	Evidence provided by one or more well-designed clinical trials, including overview (meta-analyses) of such trials	None
Class II	Evidence provided by well-designed observational studies with concurrent controls (eg, case-control and cohort studies)	None
Class III	Evidence provided by expert opinion, case series, case reports, and studies with historical controls	Prospective case series without control demonstrates safety of intraoperative RT[27] Retrospective case series of surgery plus carmustine wafer for progressive BM after prior SRS[25] Prospective phase 2 trial with historical control showed surgery + carmustine wafer (without radiation therapy) similar in terms of local control to surgery plus WBRT[26] Prospective phase I/II trial: cesium-131 beads at time of surgery safe[20] Case series: I-125 seeds implanted stereotactically[21] Retrospective review: I-125 seeds comparable to SRS for solitary BM[22-24]
Immune Therapy		
Class I	Evidence provided by one or more well-designed clinical trials, including overview (meta-analyses) of such trials	None
Class II	Evidence provided by well-designed observational studies with concurrent controls (eg, case-control and cohort studies)	None

Evidence Class	Description of Evidence Class	Associated Studies
Class III	Evidence provided by expert opinion, case series, case reports, and studies with historical controls	Retrospective case series: ipilimumab is safe in patients with melanoma BM[30-33] Phase 2 trial: ipilimumab plus fotemustine has possible activity for melanoma BM,[34] ipilimumab alone possible activity[35] Retrospective analysis of prospective data: adoptive immunotherapy is safe and has possible activity[36, 37] Case series: no evidence of activity of melanoma antigen vaccine[38]
Molecular Therapy		
Class I	Evidence provided by one or more well-designed clinical trials, including overview (meta-analyses) of such trials	RCT: afatinib has no benefit on outcome and higher toxicity in breast cancer BM[51] RCT: no role for erlotinib in treating newly diagnosed EGFR wt NSCLC BM[65]
Class II	Evidence provided by well-designed observational studies with concurrent controls (eg, case-control and cohort studies)	RCT: WBRT + SRS better than WBRT + SRS + erlotinib in terms of toxicity and outcome[64] Non-randomized controlled trial: Erlotinib + WBRT better than WBRT alone for multiple NSCLC BM[63] RCT: WBRT + gefitinib for multiple NSCLC BM has similar efficacy and better toxicity compared to WBRT + VMP[58]

Evidence Class	Description of Evidence Class	Associated Studies
Class III	Evidence provided by expert opinion, case series, case reports, and studies with historical controls	Case series: T-DM1 safe with some activity versus breast cancer BM[52] Case series: iniparib plus irinotecan safe with possible activity versus triple negative breast cancer BM[53] Case series: possible activity of trastuzumab alone[50] and with WBRT[49] for breast cancer BM Retrospective series: possible activity of lapatinib versus breast cancer BM[39, 41-44] Phase 1 trial: lapatinib plus WBRT safe[40] Retrospective series: trastuzumab may decrease incidence of breast cancer BM[41] Phase 2 trial: lapatinib monotherapy has modest activity,[45, 46] and lapatinib plus capecitabine has more activity versus BM[47, 48] Case series: bevacizumab safe in solid tumor (mostly NSCLC) BM[66-70] Case series: sunitinib safe with possible activity versus RCC BM[79] Case series: erlotinib for NSCLC BM safe with possible activity[54-57, 59, 61] Gefitinib for NSCLC BM safe with possible activity[59, 60, 62] Case series: dabrafenib has possible activity versus melanoma BM[71-73] Case series: vemurafenib has possible activity versus melanoma BM[74-78]

BM, Brain metastases; EGFR, epidermal growth factor receptor; LITT, Laser interstitial thermal therapy; NSCLC, Non-small cell lung cancer; OS, Overall survival; PFS, Progression-free survival; RCC, Renal cell carcinoma; RCT, Randomized controlled trial; SRS, Stereotactic radiosurgery; WBRT, Whole brain radiation therapy.

Table 2. Laser interstitial thermal therapy

Author, Year	Study Description	Data Class	Conclusions
Rao et al,[5] 2014	MRI-guided LITT for post-radiosurgery progression or radiation necrosis -single center, prospective Patient population: -15 patients evaluable -progressive BM or radiation necrosis -all had prior RT -followed with serial imaging Treatment regimen: LITT	III	Results: -case series, prospective, no control group -local control in 13/15 at median follow-up of 24 weeks -median PFS 37 weeks Authors' conclusions: -procedure is safe -additional studies needed to determine efficacy
Torres-Reveron et al,[4] 2013	Stereotactic LITT for recurrent brain tumors after SRS -single center Patient population: -6 patients s/p GK for BM with radiographic tumor progression -tumors deemed not resectable Treatment regimen: LITT	III	Results: -retrospective case series without control -treated area increases in size initially then decreases to smaller by 6 months; FLAIR decreases from time of procedure Author conclusions: -procedure is safe -need additional studies

Author, Year	Study Description	Data Class	Conclusions
Hawasli et al,[3] 2013	MRI guided LITT for intracranial lesions -single center case series, data collected prospectively -aim to evaluate experience with LITT patients Patient population: -17 patients with glioma, epilepsy, or progressive BM identified radiographically -5 of 17 patients had progressive BM after prior treatment (other patients had glioma or epilepsy) Treatment regimen for BM patients: -LITT to each met at time of study entry	III	Results: -prospective, case series without control/comparison group -median PFS 5.8 months -median OS also 5.8 months Author conclusions: -additional studies needed to determine clinical efficacy -safe and well-tolerated
Carpentier et al,[2] 2011	Prospective study of LITT for progressive brain metastases -Single institution pilot study Patient population: 7 patients with 15 brain mets (breast or NSCLC) refractory to chemo and radiation Treatment regimen: LITT to all mets	III	Results: -case series without control -up to 30-month follow-up -median OS 19.8 months -no tumor recurrence in ablated zones, tumor progression in non-ablated zones -no severe adverse events Author conclusions -safe treatment, phase 2/3 studies needed

BM, Brain metastases; FLAIR, Fluid-attenuated inversion recovery; GK, Gamma knife; LITT, Laser interstitial thermal therapy; NSCLC, Non-small cell lung cancer; OS, Overall survival; PFS, Progression-free survival; RT, Radiotherapy

Table 3. Radiation Sensitizers

Author, Year	Study Description	Data Class	Conclusions
Hosseini et al,[16] 2015	Prospective randomized controlled trial of WBRT ± sodium nitrite Patient population: Adult patients 18-80 years of age 20 total patients with 10 patients in each group -10 WBRT with concomitant sodium nitrite -10 WBRT alone Treatment regimen: WBRT 30 Gy x 10 fractions Sodium nitrite IV in 2 hrs 267 microg/kg/h before each radiation fraction	II	Results: -RCT -ORR 4 in SN group and 2 in WBRT alone group (p= 1.00) -In the univariate analysis, age ≥ 65 years (P = 0.05) and Presence of extracranial metastasis (p = .01) were OR predictive factors Author conclusions: -sodium nitrite did not improve radiographic response compared to WBRT alone Although a RCT, this study was classified as class II data due to low numbers of enrolled patients

Author, Year	Study Description	Data Class	Conclusions
Cao et al,[15] 2015	Phase 2 trial of WBRT with or without temozolomide for BM due to breast cancer -Randomized, prospective, multicenter Patient population: 100 patients with BM due to breast cancer -50 WBRT -50 WBRT + temozolomide Median age 50 years 40 hormone-positive, 33 triple negative, 19 HER2-positive Median follow-up 9.4 months Treatment regimen: WBRT 10-30 Gy in 3 Gy fractions Temozolomide 75 mg/m^2/day during radiation	I	Results: -prospective, randomized trial with appropriate control and reasonable numbers -47 patients (WBRT) and 37 patients (WBRT + TMZ) available for final endpoint analysis - RR - 36% (WBRT) and 30% (WBRT + TMZ) - Median OS - 11.1 months (WBRT) and 9.4 months (WBRT + TMZ) - Median PFS - 7.4 months (WBRT) and 6.8 months (WBRT + TMZ) - HER2 + OS 16.1 months (WBRT) and 20.2 months (WBRT + TMZ) - Hormone + OS 9.3 months (WBRT) and 9.4 months (WBRT + TMZ) - Hormone + PFS 6.7 months (WBRT) and 5.1 months (WBRT + TMZ) - Triple negative OS 4.9 months (WBRT) and 9.2 months (WBRT + TMZ) - Triple negative PFS 2.8 months (WBRT) and 8.0 months (WBRT + TMZ) Authors' conclusions: -TMZ did not improve local control or survival in patients with breast cancer BM

Author, Year	Study Description	Data Class	Conclusions
Shi et al,[14] 2014	Multi-institution Phase I clinical trial evaluating safety of vorinostat as radiation sensitizer in patients with BM when combined with WBRT Patient population: 17 patients with BM enrolled, 4 excluded due to disease progression or incorrect RT dose Treatment regimen: WBRT 37.5 Gy in 2.5 Gy fractions delivered over 3 weeks Daily oral vorinostat 5 days per week during course of RT Dose escalation study of vorinostat	III	Results: -multi-institution case series, no control -median OS 36 weeks -MTD vorinostat determined to be 300 mg daily -no grade 3 or 4 toxicities Author conclusions: -Treatment strategy safe -300 mg daily dose to be used in phase 2 trial
Yamazaki et al,[13] 2013	Feasibility of sanazole as radiation sensitizer for patients receiving hypofractionated SRS for recurrent BM after prior RT Patient population: 6 patients with recurrent BM after prior radiation Treatment regimen: Daily oral sanazole 1 g/day up to 2 hr prior to RT RT performed with cyberknife system	III	Results: -single institution case series with no control -no sanazole toxicities -3 PR and 3 stable disease -median OS 5 months Authors' conclusions: -treatment strategy is safe with potential to enhance efficacy of radiation

Author, Year	Study Description	Data Class	Conclusions
Rojas-Puentes et al,[12] 2013	Phase II randomized, double-blind, placebo-controlled study WBRT ± chloroquine Patient population: Adult patients age 18-80 years KPS ≥ 70 73 total patients, 39 to CLQ arm (22 MRI eval) and 34 to the placebo arm (20 MRI eval) Lung Ca 74%; Breast Ca 20.5% Median number of metastases = 3 Treatment regimen CLQ + WBRT vs placebo + WBRT WBRT 30 Gy in 10 daily fractions CLQ = 150 mg 1 hr prior to each radiation dose	II	Results: -prospective RCT with control (placebo) group -small number for an RCT Median follow-up 8.4 months Median PFS CLQ arm did not reach; placebo arm 13.3 months (p= .008) 1-yr PFS CLQ arm 83.9% and placebo arm 55.1% Median OS 8.4 months Median OS CLQ arm 10.2 months; placebo arm 7.42 months (p= .839) Median event free (progression or death) CLQ 7.5 months; placebo 7.4 months (p=0.126) Authors' conclude: -No difference in QoL between treatment arms
Eldredge et al,[19] 2013	Short course chloroquine + WBRT to treat BM -single center, prospective -endpoint was radiographic response at 3 months Patient population: -20 patients enrolled with solid tumor BM, 16 evaluable -patients had no prior RT Treatment regimen: Chloroquine 250 mg PO QD initiated 1 week prior to WBRT WBRT 37.5 Gy in 15 fractions	III	Results: - prospective but no control or comparison group -At median 5-month follow-up: 2 CR, 13 PR, 1 Stable disease -median OS 5.7 months -patients had not had prior RT so it is difficult to separate effects of chloroquine Authors' conclusions: - good control/response rate warrants additional study

Author, Year	Study Description	Data Class	Conclusions
Roberge et al,[10] 2012	Single center Phase 1 trial evaluating temozolomide as radiation sensitizer in patients with progressive BM after prior radiation undergoing SRS Primary endpoint safety Secondary endpoints include local control and OS Patient population: 26 patients with 49 BM All patients with 1-4 progressive BM after prior RT Treatment regimen: Temozolomide in 3 sequential cohorts 100 mg/m^2/day, 150 mg/m^2/day and 200mg/m^2/day administered for 5 days SRS to all BM administered on day 5 with dose depending on target diameter	III	Results: -single center, prospective, no control -no grade 3, 4 toxicities -median OS 10.2 months -local control 87.5% -Median PFS 3.3 months Authors' conclusions: -treatment strategy is safe with good local control

Author, Year	Study Description	Data Class	Conclusions
McHaffie et al,[9] 2011	Multi-institution phase II trial evaluating motexafin gadolinium + WBRT followed by SRS boost to treat up to 6 BM Primary endpoint was evaluate toxicities and feasibility Patient population: 65 patients with 1-6 BM received motexafin gadolinium + WBRT 45/65 patients received SRS boost + motexafin gadolinium Treatment regimen: WBRT 37.5 Gy in 15 fractions Patients also to receive SRS (15-21 Gy) boost within 14 days of completing WBRT Motexafin gadolinium 5 mg/kg prior to each fraction beginning with fraction 6; as well as on the day of SRS boost	III	Results: -multi-center, prospective case series -11 patients had new BM at time of SRS planning -CNS PFS and OS both 39% at 1 year -median PFS 8 months -median OS 9 months Authors' conclusions: -addition of motexafin gadolinium is safe and well-tolerated
Fogh et al,[8] 2010	Phase I study evaluating safety and efficacy of patupilone (epothilone B) + RT for CNS malignancies Study aimed to determine MTD of patupilone Patient population: Recurrent glioma (10), primary CNS tumor (5), or BM (17) Treatment regimen: BM received WBRT 37.4 Gy Dose escalation of weekly concurrent patupilone 4-week observation period after treatment	III	Results: -single center, no control -MTD determined 8 mg/m^2 every 3 weeks -median OS BM patients 23.7 months -PFS BM patients 19.2 months Authors' conclusions: -patupilone is safe at up to MTD -dose for phase II trial determined

Author, Year	Study Description	Data Class	Conclusions
Mehta et al,[7] 2009	Patient population: Adult patients with NSCLC with KPS $\geq$ 70 275 patients to WBRT alone; 279 patients to WBRT + motexafin 81% had multiple brain metastases 51% had systemic metastases Median age 59 years in each group Treatment regimen: WBRT 30 Gy x 10 fractions Motexafin 5 mg/kg/d 2-5 hours prior to each radiation dose	II	Results: -randomized controlled trial -Median to neurologic progression 10 months WBRT and 15.4 months WBRT + motexafin (p= .122) -ERC-North America-Median progression 8.8 months WBRT and 24.2 months WBRT + motexafin (p= .004) -Patients in North America received rx more promptly than the European/Australia group -North America median progression 11.8 months WBRT; 15.4 motexafin (p= .043) -Median survival 5.8 months WBRT; 5.1 months motexafin (p= 0.684) -North America median survival 5.2 months WBRT; 4.9 months motexafin (p= .938) Authors' conclusions: -favorable trend in MGd group in terms of Neurologic outcome and prolonged TTP in patients who received prompt WBRT Although this was a RCT with a good number of patients, it was downgraded due to clinical trial design. Multi-center trial in which timing of treatment not uniform ("In North American patients, where treatment was more prompt, …" results section of abstract). Additionally, although the numbers (554) are good, statistical analysis of other variables such as patient characteristics were not provided (eg multiple mets, histology, etc). Tumor burden in the brain was not provided. higher non-compliance in MGd group. Prior RT not excluded. Primary endpoint was interval to neurologic progression or death with evidence of neurologic progression.

BM, Brain metastases; CNS, Central nervous system; CQL, Chloroquine; Gy, Gray; KPS, Karnofsky performance status; MGd, Motexafin- gadolinium; MTD, Maximum tolerated dose;

NSCLC, Non-small cell lung cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PR, Partial response; QoL, Quality of life; RCC, Renal cell carcinoma; RCT, Randomized controlled trial; RT, Radiotherapy; SN, Sodium nitrite; SRS, Stereotactic radiosurgery; TMZ, temozolomide; WBRT, Whole brain radiation therapy.

Table 4. Local Therapy

Author, Year	Study Description	Data Class	Conclusions
Weil et al,[27] 2015	Feasibility of intraoperative adjuvant RT after surgical resection of newly diagnosed solitary BM Patient population: 23 patients with newly diagnosed solitary BM amenable to surgical resection Treatment regimen: Patients underwent surgical resection followed by intraoperative RT with portable radiation device 14 Gy to 2 mm depth Tumor cavity measured intraoperatively to plan radiation 15 patients received subsequent radiation (SRS, WBRT or both)	III	Results: -prospective case series without control -5-year minimum follow-up -mean PFS of surgical site 22 months Authors' conclusions: - treatment strategy is safe with local control rates comparable to other techniques
Mu et al,[25] 2015	Single institution, retrospective case series Surgery with carmustine wafer implantation as salvage therapy after local failure of SRS for BM Assessed local control, OS, toxicity and cause of death Patient population: 31 patients s/p SRS for BM with radiographic evidence of progression Treatment regimen: Surgery for tumor resection and implantation of carmustine wafers Serial imaging and neurologic examinations	III	Results: -retrospective case series with no control/comparison group -OS at 6 months – 63%, 12 months – 36% -local control 6 months – 87%, 12 months – 70% -most patients had linear enhancement on postoperative MRI -toxicities: 3 hydrocephalus requiring VPS, 1 CSF leak, 1 infection, 3 HA Authors' conclusions: - treatment strategy is effective salvage therapy for local control after tumor recurrence

Author, Year	Study Description	Data Class	Conclusions
Wernicke et al,[20] 2014	Single center phase I/II trial of cesium-131 permanent brachytherapy at the time of surgical resection of brain metastasis in lieu of WBRT Primary endpoint is local control, also evaluated distant CNS BM, toxicity and OS Patient population: 24 patients with newly diagnosed BM Treatment regimen: Dominant BM surgically resected and cesium-131 beads implanted permanently Other lesions treated with SRS or WBRT depending on number	III	Results: -prospective case series without control -1-year local control 100% -1-year regional control 93% -median OS 9.9 months -no radiation necrosis -CSF leak, infection (1 each) Authors' conclusions: - treatment regimen is safe with good local control
Brem et al,[26] 2013	Multi-center phase 2 trial involving surgery + carmustine wafer for BM with WBRT deferred Goal was to evaluate for preservation of neurocognitive function and local control Patient population: 59 patients who underwent surgery for solitary or dominant (max 3 lesions) BM Patients with multiple lesions received SRS to other lesions Treatment regimen: Surgery for resection of solitary or dominant BM with placement of carmustine wafers into cavity	III	Results: -prospective study with local control rates compared with historical data -improvements in neurocognitive function -local control 78% at 1 year; comparable to historical control rates with surgery + WBRT and better than WBRT alone Authors' conclusions: - carmustine wafers are safe and similarly effective compared to WBRT after surgery -RCT needed to evaluate neurocognitive function and local control to determine if treatment algorithm improves outcomes

Author, Year	Study Description	Data Class	Conclusions
Ruge and Kickingereder et al,[21] 2011	Stereotactic biopsy and placement of I-125 seeds for local recurrence of BM after SRS (salvage therapy) Single center case series Patient population: 30 patients with radiographic progression of BM after prior SRS 27 received brachytherapy seeds after intraoperative confirmation of viable tumor Patients not candidates for surgical resection All had undergone prior local therapy for the tumor and had radiographic evidence of local failure Treatment regimen: Surgery for stereotactic biopsy If intraoperative pathology consult indicates viable tumor, I-125 seeds placed during the same surgery Seed catheters require explantation 1.5 months later	III	Results: -case series with no control or comparison group -no grade 3 or 4 toxicity -median OS 14.8 months -9 patients died in first 4.5 months -Of remaining 18 patients, 14 developed CNS failure, but only 1 developed local failure -1 year local PFS 93.3% and distant PFS 54.5% Authors' conclusions: - SBT is safe and effective, especially in patients with possible radiation necrosis or larger tumors not amenable to surgical resection

Author, Year	Study Description	Data Class	Conclusions
Ruge and Kocher et al,[22] 2011	Comparison of I-125 SBT to SRS for treatment of solitary BM Retrospective, single-center study Patient population: 219 patients with solitary brain metastases deemed either surgically unresectable or not space occupying Patients underwent SBT if tumors were >14 cc, if histology was needed, or if the radiographic finding represented local recurrence after SRS Treatment regimen: 142 patients underwent SRS to treat solitary BM (LINAC based) 77 patients underwent SBT to treat solitary BM – stereotactic surgery involving biopsy of tumor and implantation of I-125 seeds	III	Results: -comparison of 2 treatment strategies with good numbers and no significant epidemiologic or demographic differences -no differences in median OS, local control, or CNS control between treatment groups Authors' conclusions: - SBT is a viable treatment strategy with advantages including the ability to treat larger volumes and sample the tumor at the time of seed implantation -Results from SBT comparable to SRS, but these patients started at somewhat of a disadvantage (larger tumor, possible SRS failure)
Ruge and Suchorska et al,[23] 2011	Retrospective review I-125 seeds for solitary BM -retrospective, single-center Patient population: -90 patients with solitary BM (various histology) -29 had prior brain treatment (21 WBRT) Treatment regimen: -stereotactic biopsy and implantation of I-125 seeds	III	Results: -no treatment-related mortality -3.3% morbidity -Median OS 8.5 months (18.1 months for RPA class 1 patients) -1-year PFS 94.6% Authors' conclusions: -SBT safe with results similar to SRS and surgery

Author, Year	Study Description	Data Class	Conclusions
Huang et al,[24] 2009	Retrospective single center review Evaluate efficacy of surgery + permanently implanted I-125 beads (brachytherapy) without WBRT for BM Patient population: 40 patients with surgically resectable BM (solitary or dominant, if multiple) 19 new, 21 recurrent (s/p surgery, WBRT and/or SRS) Any primary pathology included Treatment regimen: -All 40 patients underwent surgical resection of dominant lesion(s) with I-125 beads permanently placed in walls of resection cavity. -Patients with multiple lesions had dominant lesion(s) treated with treatment algorithm and other lesions received SRS near time of surgery if not previously treated	III	Results: -retrospective review of case series without control group or comparison group -median OS 11.3 months (12 with newly diagnosed BM, 7.3 in recurrent BM) -1-year local control 88% -symptomatic radiation necrosis in 23% Authors' conclusions: - data supports brachytherapy for newly diagnosed or symptomatic recurrent BM -Would need comparison with SRS to evaluate efficacy
Aziz et al, 2009[28]	Case series of patients who underwent surgery for BM followed by intraoperative photodynamic therapy to the resection cavity Patient population: 14 patients underwent surgery for resection of BM (7 NSCLC, 7 'other') then PDT intraoperatively No prior treatment for BM All patients followed until death Treatment regimen: Surgery for BM resection and intraoperative photodynamic therapy	III	Results: -retrospective review of prospectively collected data -no control group or comparison -2/14 patients died of progressive BM (none of the 7 with NSCLC); 7/14 died of systemic disease Authors' conclusions: -Results support efficacy of treatment strategy and warrant further study -excellent results for NSCLC BM population

BM,Brain metastases; CNS, Central nervous system; CSF, Cerebrospinal fluid; Gy, Gray; MRI, Magnetic resonance imaging; NSCLC, Non-small cell lung cancer; OS, Overall survival; PDT,

Photodynamic therapy; PFS, Progression-free survival; RCT, Randomized controlled trial; RPA, Recursive partitioning analysis; RT, Radiotherapy; SBT, Stereotactic brachytherapy; SN, Sodium nitrite; SRS, Stereotactic radiosurgery; WBRT, Whole brain radiation therapy

Table 5. Immune Modulators

Author, year	Study Design	Data Class	Conclusions
Kiesset al,[30] 2015	-SRS for melanoma BM in patients receiving ipilimumab -single center, retrospective Patient population: -46 patients with 113 BM due to melanoma underwent SRS in the setting of ipilimumab therapy Treatment regimen: -median 4 doses of ipilimumab -SRS median dose 21 Gy -safety and survival analyzed	III	Results: -retrospective study without controls -unclear effects of ipilimumab on BM since all patients treated with SRS also -1-year OS with SRS during ipilimumab (65%), before ipilimumab (56%), and after starting ipilimumab (40%) -SRS during ipilimumab trended towards improved local control -Grade 3-4 toxicity in 20% of patients Authors' conclusions: -SRS treatment during or before ipilimumab associated with improved OS compared with SRS after initiation of ipilimumab -SRS + ipilimumab is safe and concurrent SRS + ipilimumab may confer improved local control and OS

Author, year	Study Design	Data Class	Conclusions
Jones et al,[31] 2015	Ipilimumab + surgery for melanoma BM -single center, retrospective chart review -question was does surgery help to relieve intracranial tumor burden allowing for effects of ipilimumab, which can take 3 months (ie, surgery as a bridge to ipilimumab) Patient population: -12 patients who received ipilimumab and underwent craniotomy within 3 months of initiation of ipilimumab -all also received adjuvant RT -median 4 doses of ipi Treatment regimen: -ipilimumab + surgery for melanoma BM	III	Results: -Retrospective review without control -RT also used and makes data difficult to evaluate for effects of ipilimumab -11/12 patients stopped ipilimumab due to disease progression -results do not support clinical activity of ipilimumab -median OS 7 months Authors' conclusions: -surgery is safe in setting of ipilimumab
Gerber et al,[32] 2015	Ipilimumab + WBRT for melanoma BM -retrospective single center study -goal to evaluate safety of treatment algorithm Patient population: -13 consecutive patients with melanoma BM treated with WBRT within 30 days of initiation of ipilimumab -median 7 BM -median follow up 4 months Treatment regimen: -ipilimumab 3 mg/kg, 2-4 doses -WBRT median 30 Gy, median 10 fractions -radiographic response evaluated by serial MRI	III	Results: -retrospective study with no controls -all patients had radiographic evidence of hemorrhage -low adverse event rate (1 patient with grade 3-4 toxicity) -4/9 evaluable for radiographic response had stable disease or PR Authors' conclusions: -authors conclude primary pattern of CNS response to ipilimumab + WBRT is stable disease -unclear if added effect from ipi to WBRT but treatment strategy appears safe

Author, year	Study Design	Data Class	Conclusions
Zhang et al,[37] 2014	Adoptive immunotherapy for NSCLC by NK and cytotoxic T lymphocytes mixed effector cells -Retrospective, single center Patient population: 108 patients with NSCLC divided into 2 groups -54 had adoptive NKTm cellular immunotherapy (no surgery, chemo, or RT) --14 of these 54 had BM -54 received surgery, chemo, or RT --13 of these 54 patients had BM Treatment regimen: At time of data collection, 54 patients had received adoptive immunotherapy while 54 patients had received standard therapy (surgery, chemo, RT) Patients subsequently treated per clinician choice	III	Results: -retrospective, case-control -median OS patients with BM --immunotherapy group 19.6 months --control group 22.7 months --no other data able to be gleaned regarding BM patients Authors' conclusions: -treatment strategy effective in terms of prolonging survival for NSCLC patients -No specific comment regarding BM patients
Queirolo et al,[29] 2014	Ipilimumab for compassionate use in patients with metastatic melanoma who do not qualify for a clinical trial -Prospective multicenter study -Expanded access program in Italy Patient population: -855 patients in study, 146 with asymptomatic BM -MRI brain not required to enter study (may have missed some BM patients) Treatment regimen: -ipilimumab 3 mg/kg every 3 weeks for 4 cycles	III	Results: -prospective data, retrospectively analyzed; large number but no control or comparison group -median follow-up of BM patients 20 months -4/145 CR, 13/145 PR, 22/145 stable disease -median duration of response 9.7 months -median time to onset of response 3.4 months for CR, 3.0 months for PR -median OS 4.3 months, median PFS 2.8 months -29% patients with treatment-related AE -1-year survival 20% Authors' conclusions: -ipilimumab shows durable benefits in some patients with BM

Author, year	Study Design	Data Class	Conclusions
Di Giacomo, 2012[34]	Ipilimumab + fotemustine for melanoma -single arm phase 2 trial -multicenter Patient population: -86 total patients, 20 with asymptomatic BM -maximum 1 prior chemotherapy agent -primary endpoint was immune related disease control Treatment regimen: -induction 10 mg/kg ipilimumab every 3 weeks for 4 doses and 100 mg/m^2 fotemustine weekly for 3 weeks then every 3 weeks for weeks 9-24 -if clinical response noted, patients could continue ipilimumab every 12 weeks and fotemustine every 3 weeks	III	Results: -prospective, no control arm or comparison group -10/20 BM patients had disease control; 2 of these were CR -55% had treatment related AE -prior studies on monotherapy of both agents used for statistical analysis and study planning Authors' conclusions: -treatment regimen shows clinical activity in patients with melanoma BM
Tarhini et al,[38] 2012	Safety and efficacy of melanoma antigen vaccines using MART-1, gp100 and tyrosinase -prospective single center Patient population: -22 stage IV melanoma patients enrolled, 20 evaluable -8 patients had BM, all previously treated Treatment regimen: -multi-epitope peptide vaccine containing MART-1, gp100 and tyrosinase given with immunomodulators GM-CSF and PF3512676 -peripheral antigen specific T cells measured at 50 and 90 days -mean 3.5 vaccination cycles per patient	III	Results: -prospective but no control/comparison group for the BM patients; historical control data mentioned for OS/PFS for systemic disease -7/8 patient with BM showed progression of disease during follow-up period (90 days) -no treatment-related toxicities -median PFS 1.9 months, median OS 13.4 months Authors' conclusions: - regimen is safe and worth further investigation -BM-specific data not fully discussed but results available do not support significant activity

Author, year	Study Design	Data Class	Conclusions
Margolin et al,[35] 2012	Ipilimumab for patients with melanoma BM Phase 2 trial multicenter Patient population: Cohort A: (n= 51) asymptomatic, no steroids at study entry Cohort B: (n= 21) neurologically symptomatic on stable steroid dose Treatment regimen: 4 doses 10 mg/kg ipilimumab every 3 weeks; if clinically stable then start ipilimumab 10 mg/kg every 12 weeks	III	Results: -prospective, no control -At 12 weeks, 12 patients in cohort A (24%) and 2 patients in cohort B (10%) had disease control with respect to BM Author conclusions: - ipilimumab has some activity in BM, especially if small and asymptomatic, with expected toxicities
Weber et al,[33] 2011	Ipilimumab in patients with melanoma BM Retrospective analysis of prospective data collected as part of phase 2 trial multicenter Patient population: Of 115 patients in the clinical trial, 12 had stable BM at time of enrollment Treatment regimen: Ipilimumab 10 mg/kg	III	Results: -retrospective, no control -2/12 PR, 3/12 SD -both PR patients and 1 SD patient had survival > 4 years -median OS 14 months -CNS adverse events in 2 patients Authors' conclusions: -ipilimumab safe and has efficacy in some patients with stable BM due to melanoma

Author, year	Study Design	Data Class	Conclusions
Hong et al,[36] 2010	ACT with autologous antitumor lymphocytes plus IL-2 Patient population: -prospective trial of 264 metastatic melanoma patients -subset of BM patients (n= 26) retrospectively analyzed Treatment regimen: - 26 patients with BM received ACT followed by either: --- infusion of autologous tumor-infiltrating lymphocytes (n= 17) Or ---autologous lymphocytes retrovirally transduced to express T-cell receptor that recognized melanoma antigens gp-100 or MART-1 (n= 9)	III	Results: -prospective, but no control patients -variations among patients included RT in some, varying doses of IL-2 -7/17 who received ACT with tumor infiltrating lymphocytes had CR of BM; median OS 8.5 months -2/9 with T cell receptor-transduced lymphocytes had CR of BM; median OS 15 months Authors' conclusions: -complete and durable response of BM in some patients warrant additional study

ACT, adoptive cell transfer; AE, Adverse event; BM, Brain metastases; CNS, Central nervous system; Gy, Gray; IL-2, interleukin-2; MRI, Magnetic resonance imaging; NSCLC, Non-small cell lung cancer; OS, Overall survival; PFS, Progression-free survival; RT, Radiotherapy; SRS, Stereotactic radiosurgery; WBRT, Whole brain radiation therapy

Table 6. Molecular Targeted Therapy

Author, Year	Study Description	Data Class	Conclusions
Wang et al,[58] 2015	Gefitinib vs VMP + WBRT to treat multiple BM due to NSCLC -Prospective, randomized -Single center Patient population: 73 patients with BM due to NSCLC Treatment regimen: -WBRT plus either -- gefitinib alone (n= 37) or --VM-26 at 100 mg/day days 1-3 and cisplatin 25 mg/m2 day 1-3, 1 cycle = 21 days (n= 36)	II	Results: -prospective with control -lower toxicities with gefitinib group -median OS gefitinib group 13.3 months, VMP group 12.7 months -response rate 56% in gefitinib group and 47% VMP group -no differences in gefitinib group based on EGFR status Authors' conclusions: - gefitinib is a valid choice for these patients given similar efficacy and lower toxicity -warrants larger randomized trial Although an RCT, this trial was downgraded due to somewhat small numbers (n= 73), as well as little data regarding patient characteristics. Trial geared toward 2-month post-RT radiographic response and overall survival with minimal other data.
Harding et al,[78] 2015	Vemurafenib as treatment for melanoma BM Retrospective, single center Patient population: Among 140 patients reviewed, 27 patients had BRAF mutant melanoma BM and were subsequently treated with vemurafenib 27 were available for survival analysis; 22 evaluable for response Lesions previously treated with surgery or SRS excluded as targets for analysis Treatment regimen: Vemurafenib 960 mg BID	III	Results: -retrospective, no control -intracranial response rate 50% -median intracranial PFS 4.6 months -median OS 7.5 months Author conclusions: - vemurafenib is active in patients with BRAF mutant melanoma with BM and warrants further studies -good cns response, warrants further studies

Author, Year	Study Description	Data Class	Conclusions
Cortes et al,[51] 2015	Afatinib or afatinib + vinorelbine or investigator choice to treat HER2+ breast cancer with BM during or after trastuzumab and/or lapatinib Phase 2, randomized clinical trial Multicenter Patient population: 121 patients with HER2+ breast cancer with BM Treatment regimen: 40 afatinib 40 mg PO QD or 38 afatinib 40 mg QD + Vinorelbine 25 mg/m^2 once per week or 43 investigator choice therapy Treatment continued until disease progression or toxicity	I	Results: -randomized prospective trial -patients receiving afatinib based therapy did not have improvement in outcomes -afatinib associated with higher rate of toxicity Authors' conclusions: -no further development of afatinib in this disease should be considered

Author, Year	Study Description	Data Class	Conclusions
Besse et al,[70] 2015	Non-randomized phase 2 study of bevacizumab for treatment of asymptomatic BM due to NSCLC -Evaluate safety and efficacy -Primary endpoint 6-month PFS Patient population: Asymptomatic, untreated BM in patients who are chemo naïve or pretreated Treatment regimen: B+CP = bevacizumab + carboplatin/paclitaxel B+E= bevacizumab + erlotinib -67 patients received B + CP: ---First-line bevacizumab 15 mg/kg plus ---Carboplatin area under curve x 6 plus paclitaxel 200 mg/m^2 every 3 weeks -24 patients received B + E: (patients had failed platinum-based therapy) ---Second-line bevacizumab plus ---Erlotinib 150 mg/day	III	Results: -cannot truly compare groups given differences in patient presentation -6 months PFS for B+CP 56.5%, median PFS 6.7 months, median OS 16 months, overall response rate 61.2% for intracranial lesions -6-month PFS for B+E 57.2%, median PFS 6.3 months, median OS 12 months, overall response rate 12.5% Author conclusions: - treatment regimen shows encouraging efficacy and safety of B+CP -numbers low in comparison group and difficult to evaluate given use of second molecular targeted agent

Author, Year	Study Description	Data Class	Conclusions
Bartsch at al,[52] 2015	T-DM1 in HER2+ breast cancer BM -Prospective, single center T-DM1 = antibody drug conjugate linking trastuzumab to cytotoxic anti-microtubule agent (DM1) Patient population: -10 patients with newly diagnosed asymptomatic (n= 2) HER2+ breast cancer BM or progressive BM after local therapy (n= 8) -All had received prior trastuzumab; 6 had received lapatinib; 3 had received pertuzumab Treatment regimen: T-DM1 3.6 mg once every 3 weeks MRI every 12 weeks	III	Results: -case series with no control -3 partial response -2 stable disease for > 6 months -intracranial PFS 5 months Authors' conclusions: -T-DM1 has some activity vs BM but L + C remains best option if local therapy fails and that further studies are warranted (L + C = lapatinib + capecitabine)
Ahmed et al,[77] 2015	LINAC-based SRS + vemurafenib for melanoma BM -Retrospective review -Single institution -Evaluation of safety of treatment strategy Patient population: 24 patients with 80 melanoma BM treated with SRS while on vemurafenib Treatment regimen: -Median SRS dose 24 Gy -Vemurafenib 960 mg BID – drug held 2-3 days before and after SRS	III	Results: -retrospective case series without control -6-month local control 92% -12-month local control 75% -14 patients had distal BM at median 3.4 months after SRS -median OS from SRS 7.2 months -no significant toxicity Authors' conclusions: -SRS during vemurafenib therapy is safe -unable to make statement on efficacy of vemurafenib

Author, Year	Study Description	Data Class	Conclusions
Zustovich et al,[69] 2014	Bevacizumab-based therapy for patients with BM due to NSCLC -Single center Patient population: 13 patients with clinical and radiographic progressive BM due to NSCLC Treatment regimen: -Bevacizumab 7.5 mg/kg and cisplatin 75 mg/m^2 day 1 -Gemcitabine 1250 mg/m^2 day 1 and 8 21-day cycle	III	Results: -prospective, case series without control -PFS 9.1 months -OS 9.6 months Author conclusions: -treatment regimen was safe with encouraging PFS and OS -unclear effects of bevacizumab given multiple agents used in regimen
Levy et al,[68] 2014	Phase I study of bevacizumab + WBRT for BM due to solid tumors -Multicenter, prospective, no control Patient population: 19 patients (13 breast cancer) Treatment regimen: 3 + 3 dose escalation design Dose levels 0-2: -(bevacizumab 5, 10, 15 mg/kg every 2 weeks) -WBRT 30 Gy in 15 fractions dose level 3 - bevacizumab 15 mg/kg every 2 weeks -WBRT 30 Gy in 10 fractions	III	Results: -prospective case series without control -no dose-limiting toxicities -PR of BM in 10/19 patients: 1/3 at dose level 0, 2/3 at dose level 1, 2/3 at dose level 2 and 6/7 at dose level 3 Authors' conclusions: -treatment regimen is safe and recommended clinical trials using dose level 3

Author, Year	Study Description	Data Class	Conclusions
Lee et al,[65] 2014	Erlotinib + WBRT for NSCLC BM Randomized, multicenter Patient population: 80 patients with untreated, newly diagnosed NSCLC BM randomized to placebo (n= 40) or erlotinib (n= 40) Treatment regimen: WBRT 20 Gy in 5 fractions Erlotinib 100 mg QD given concurrently with WBRT	I	Results: -randomized, prospective with placebo control -median PFS 1.6 months in both groups -low frequency of EGFR mutation (1/35) Author conclusions: - no role for erlotinib in patients with EGFR wild-type NSCLC with BM
Dzienis et al,[76] 2014	Vemurafenib for BRAF-mutant melanoma BM -Retrospective, single center Patient population: 22 patients with BRAF mutant melanoma asymptomatic BM -12 had no prior local therapy for BM (group A) -6 had prior surgery or RT with residual disease (group B) -4 had prior local therapy but now with progression (added to group A so total group A = 16 Treatment regimen: Vemurafenib 960 mg BID	III	Results: -retrospective case series, no control -50% local radiographic response of BM in group A and group B -median time to CNS progression in all patients 23 weeks in responding patients and 14 weeks in non-responders -median OS 46 weeks in responders and 21 weeks in non-responders -20/22 had CNS progression at or before systemic progression Authors' conclusions: - additional studies warranted given 50% response rate

Author, Year	Study Description	Data Class	Conclusions
Dummer et al,[75] 2014	Vemurafenib for symptomatic BRAF mutant melanoma BM -Pilot study evaluating safety -Multi-center, prospective Patient population: -24 patients with non-resectable BM due to BRAF mutant melanoma Treatment regimen: Vemurafenib 960 mg BID	III	Results: -single center, prospective, no control -median treatment duration 3.8 months and most discontinued due to progression -4 patients developed cutaneous squamous cell carcinoma -median PFS 3.9 months -median OS 5.3 months -10 patients with PR Authors' conclusions: -vemurafenib has activity vs melanoma BM with BRAF mutation and that the treatment is safe -need prospective trials
Azer et al,[73] 2014	Evaluation of patterns of response and progression in patients with BM due to BRAF mutant melanoma treated with dabrafenib Prospective data collection, single institution Data part of phase 1 and 2 trials Patient population: 23 patients with BRAF mutant melanoma with BM -12 patients no prior treatment for BM -11 patients had prior local therapy and now with progression Treatment regimen: Dabrafenib 150 mg BID	III	Results: -case series with no control -intracranial response rate 78% -median PFS 23.6 weeks Authors' conclusions: -intracranial and extracranial disease responds similarly to dabrafenib -dabrafenib seems to have activity and further studies warranted

Author, Year	Study Description	Data Class	Conclusions
Anders et al,[53] 2014	Phase 2 study of iniparib + irinotecan to treat progressive triple negative (ER, PR, HER2) breast cancer BM multicenter Patient population: 37 patients with new or progressive BM due to triple negative breast cancer (34 evaluable) Cohort 1: progressive BM after RT Cohort 2: new, RT naïve BM not in urgent need of local therapy Treatment regimen: Irinotecan 125 mg/m^2 on days 1 and 8 of a 21-day cycle Iniparib 5.6 mg/kg on days 1, 4, 8, and 11	III	Results: -no control, case series -median PFS 2.14 months -median OS 7.8 months -intracranial response rate 12% -treatment well tolerated -unclear how to partition effects of iniparib since given with irinotecan Authors' conclusions: -modest activity of iniparib + irinotecan for BM due to triple negative breast cancer

Author, Year	Study Description	Data Class	Conclusions
Zustovich et al,[67] 2013	Bevacizumab as front-line treatment for brain metastases Bevacizumab + chemo or IFN-alpha as first therapy for BM not candidates for local therapy Serial MRI and evaluation for toxicities, OS Patient population: 18 patients with BM (mostly lung and RCC) Most were treatment naïve for BM Treatment regimen: NSCLC: 21 day cycles; 6 total cycles then maintenance bevacizumab Bevacizumab 7.5 mg/kg or 15 mg/kg day 1 Cisplatin 75 mg/m2 day 1 Gemcitabine 1250 mg/m^2 day 1 and 8 RCC: following treatment every 2 weeks until disease progression Bevacizumab 10 mg/kg IFN-alpha 3 MIU 3x/wk	III	Results: -prospective case series without control -60% PR, 40% stable disease -PFS 14 months -OS 15 months Authors' conclusions: -use of bevacizumab is feasible in these patients and efficacy data encouraging -toxicities: 2 strokes, 1 pulmonary embolism, 1 gastric ischemia -possible activity but larger study warranted

Author, Year	Study Description	Data Class	Conclusions
Zhuang et al,[63] 2013	WBRT with or without erlotinib for patients with multiple BM due to NSCLC -Single center Patient population: 31 patients in WBRT group, 23 patients in WBRT + erlotinib group All with multiple BM due to NSCLC not previously treated Patients who underwent EGFR mutation status testing regardless of result assigned to erlotinib group No EGFR testing assigned to WBRT alone group Treatment regimen: WBRT 30 Gy in 10 fractions Erlotinib 150 mg QD starting first day of RT and continuing 1 month past the end of RT	II	Results: -non-randomized, single center with control group -response rate 55% in WBRT group and 96% in WBRT + erlotinib group -median local PFS 6.8 vs 10.6 months (WBRT alone vs WBRT + erlotinib) -median OS 8.9 months vs. 10.7 months (WBRT alone vs WBRT + erlotinib) -no differences in erlotinib group based on EGFR status Authors' conclusions: -erlotinib prolongs PFS and OS compared with WBRT alone with acceptable toxicity profile -data supports activity of erlotinib in BM due to NSCLC
Yomo et al,[39] 2013	Molecular targeted therapy and SRS for HER2+ breast cancer brain metastases Retrospective, single center Patient population: 80 patients with 707 BM underwent SRS for breast cancer BM -40 patients with HER2+ breast cancer --24/40 received lapatinib-based therapy --16/40 non-lapatinib-based therapy Treatment regimen: Gamma knife, median dose 20 Gy Lapatinib dose not mentioned	III	Results: -retrospective with control group -lapatinib-based therapy associated with improved local control (86% vs 69% 1-year local control) Authors' conclusions: - data show synergy between lapatinib and SRS in treating HER2+ breast cancer BM and that lapatinib therapy is associated with improved outcomes

Author, Year	Study Description	Data Class	Conclusions
Wu et al,[57] 2013	Erlotinib as second-line therapy for metastatic NSCLC with asymptomatic BM Phase 2 trial evaluating efficacy (primary endpoint PFS) Patient population: 48 patients with lung adenocarcinoma or EGFR mutant NSCLC with asymptomatic BM after prior platinum-based therapy Treatment regimen Erlotinib 150 mg/day		Results: -prospective case series without control -median PFS 10.1 months (intracranial) -EGFR mutant median PFS 15.2 months compared with EGFR wild type 4.4 months -median OS 18.9 months Authors' conclusions: -single agent erlotinib active versus NSCLC BM and well tolerated
Welsh et al,[61] 2013	Phase 2 trial of erlotinib + WBRT for NSCLC BM Multicenter Patient population: 40 patients with BM due to NSCLC BM newly diagnosed History of prior craniotomy or SRS okay Treatment regimen: WBRT 30 Gy in 10 fractions first 10 patients then 35 Gy in 14 fractions for remaining patients Erlotinib 150 mg QD for 6 days then QD during WBRT and after until disease progression	III	Results: -prospective case series without control -86% demonstrated CNS response -no grade 4 or greater toxicity -median OS 11.8 months (9.3 months for EGFR wild-type, 19.1 months with EGFR mutant) Authors' conclusions: -treatment strategy well tolerated with favorable objective response rate

Author, Year	Study Description	Data Class	Conclusions
Sperduto et al,[64] 2013	Randomized, phase III controlled trial to evaluate SRS alone vs SRS and WBRT with temozolomide or Erlotinib in NSCLC Multicenter Patient population: 381 adult patients ≥18 years of age with 1-3 brain metastases ≤ 4 cm KPS 70-100; stable systemic disease with no evidence 1 month prior to enrollment 125 patients enrolled from 28 institutions Median follow-up was 33.6 months for 20 patients still alive (16%) Treatment regimen: Arm 1: WBRT plus SRS Arm 2: WBRT plus SRS plus Temozolomide Arm 3: WBRT plus SRS plus Erlotinib WBRT 1 week after randomization 2.5 Gy x 15 fractions (37.5 Gy) SRS given up to 14 days after WBRT completion SRS: < 2 cm 24 Gy, 2.1 - 3 cm 18 Gy, 3.1 - 4 cm 15 Gy Optic nerve, brainstem, and chiasm < 8 Gy and motor strip < 15 Gy Temozolomide 75 mg/m^2/dy for 21 days with WBRT. Discontinued or 150 mg/m^2/day 5 days/month for 6 months Erotinib 150 mg/day with WBRT or after radiation could be continued up to 6 months	II	Results: -multicenter prospective trial with control -TMZ nor ETN w/ WBRT/SRS increased OS or time to -CNS progression compared with WBRT/SRS alone -Median survival time WBRT/SRS 13.4 months, TMZ 6.3 months, ETN 6.1 months -CNS progression rates WBRT/SRS 16%, TMZ 29%, ETN 20% -Median CNS PFS 8.1 month, 4.6 months, 4.8 months -Deterioration rate of performance status at 6 months 53%, 86%, 86% -Rate of death from neurologic cause 17%, 15%, 19% -Serious grade 3-5 toxicities 11%, 41%, 49% Authors' conclusions: - addition of erlotinib or temozolomide to WBRT + SRS did not improve survival and may have been Deleterious, but that study is underpowered

Author, Year	Study Description	Data Class	Conclusions
Narayana et al,[74] 2013	Vemurafenib and RT for melanoma BM Single center, retrospective Patient population: 12 patients with V600 mutant melanoma 8 harboring BM Treatment regimen: Vemurafenib 960 mg BID SRS or WBRT during or before vemurafenib	III	Results: -retrospective, no control -radiographic responses noted in 36/48 BM with 23 CR -6-month local control 75% Authors' conclusions: - patients with BM due to V600 mutant melanoma may respond well to vemurafenib -study too small and confounded by use of RT
Lin et al,[40] 2013	Phase 1 study of lapatinib + WBRT for HER2+ breast cancer BM Study designed to determine MTD of lapatinib given with RT Multi-center Patient population: 35 patients enrolled with HER2 positive breast cancer with at least 1 BM Treatment regimen: Lapatinib 750 mg BID on day 1 then 1000, 1250 or 1500 mg daily WBRT 37.5 Gy in 15 fractions After WBRT patients received trastuzumab 2 mg/kg weekly and lapatinib 1000 mg daily	III	Results: -prospective, no control -CNS response rate among 28 evaluable patients 79% -6 month PFS 46% -unclear contribution from lapatinib since RT used Authors' conclusions: - frequent toxicities but some activity warrant consideration for future clinical trials with careful safety monitoring
Lim et al,[79] 2013	RCC BM treated with sunitinib without local therapy Retrospective, single center Patient population: 6 patients with RCC BM without prior surgery or RT Treatment regimen: Sunitinib dose not given	III	Results: -retrospective, no control group -2 patients with near complete response in brain, durable for 23 and 47 months -data largely anecdotal and further clinical data needed to assess activity of sunitinib vs RCC BM Authors' conclusions: -treatment regimen safe and warrants further work

Author, Year	Study Description	Data Class	Conclusions
Iuchi et al,[60] 2013	Gefitinib alone without RT for patients with EGFR mutant NSCLC with newly diagnosed BM Single center Patient population: 41 patients with EGFR mutant NSCLC with newly diagnosed BM not previously treated with RT and no history of TKI Treatment regimen: Gefitinib 250 mg PO QD until disease progression Brain MRI performed 1 month after treatment initiation and then every 2 months After tumor progression, patients given erlotinib Radiation used as salvage after progression on erlotinib	III	Results: -response rate 87.8% -single center, case series without control -median PFS 14.5 months -median OS 21.9 months -exon 19 deletion associated with improved PFS and OS Authors' conclusions: - BM due to EGFR mutant NSCLC responds favorably to gefitinib, especially the exon 19 deletion patients -no grade 4 toxicities
Berghoff et al,[41] 2013	Impact of switching to lapatinib or staying on trastuzumab in patients with HER-2+ metastatic breast cancer Single center, retrospective review Patient population: 201 patients with progressive metastatic breast cancer 11 patients had BM Treatment regimen: -115 received multiple lines of trastuzumab based therapy (19 received lapatinib) -58 received trastuzumab alone -28 control patients prior to trastuzumab use	II	Results: -retrospective review but with control population and large number Trastuzumab improved OS compared to control Adding lapatinib did not improve OS when all patients analyzed Subset of patients with BM showed improved OS with addition of lapatinib -lapatinib: 6 patients with BM had 22 mo OS -trastuzumab: 60 patients developed BM had 5-month OS -control: 16 developed BM Trastuzumab showed trend towards decrease in developing BM Authors' conclusions: -lapatinib may improve OS in patients with HER-2+ breast cancer BM

Author, Year	Study Description	Data Class	Conclusions
Bachelotet al,[47] 2013	Lapatinib + capecitabine for previously untreated HER2+ breast cancer BM Phase 2 trial Multi-institution Primary endpoint CNS response Patient population: 45 patients with newly diagnosed untreated BM due to HER2+ breast cancer No prior RT 44 assessable Treatment regimen: Lapatinib 1250 mg PO daily Capecitabine 2000 mg/m2 days 1-14 21-day cycle	III	Results: -no control, prospective -29/44 had CNS response > 50% volume reduction in BM -all were PR (no CR) -49% had grade 3 or 4 event -4 patients discontinued treatment due to toxicity Authors' conclusions: -L + C is active vs BM and that phase 3 trial is warranted -unclear the contributions of lapatinib and capecitabine to activity vs BM – for purposes of evaluating molecular targeted agents, evaluation of lapatinib is most relevant
Pesce et al,[62] 2012	Patients with BM due to NSCLC treated with WBRT and gefitinib or temozolomide Outcome, QOL and cognitive function Randomized phase 2 trial Multicenter Patient population: 59 patients with multiple BM due to NSCLC Treatment regimen: WBRT 30 Gy in 10 fractions 16 gefitinib 250 mg QD 43 temozolomide 75 mg/m^2 on 21/28 days	III	Results: -randomized, comparison of agents -median OS gefitinib group 6.3 months -median OS temozolomide group 4.9 months -median time to neurologic progression -gefitinib 4.8 months -temozolomide 8 months -shorter time to CNS progression and higher rate of CNS progression in gefitinib group Authors' conclusions: -survival of both groups unsatisfactory and data do not support use of either treatment regimen for this patient population

Author, Year	Study Description	Data Class	Conclusions
Parket al,[59] 2012	Efficacy of EGFR TKI in patients with specific EGFR mutant (exon 19 or 21) NSCLC with BM Prospective, single institution, phase 2 trial Patient population: 28 patients with EGFR mutant NSCLC with BM and no prior local therapy (eg, WBRT or SRS) Treatment regimen: 6 erlotinib 150 mg/day or 22 gefitinib 250 mg/day	III	Results: -prospective case series without control -23/28 patients showed partial response -median PFS 6.6 months and median OS 15.9 months -no differences in PFS and OS between erlotinib and gefitinib -local therapy free interval of 12.6 months -among 21 progressions, 17 involved intracranial progression -22 gefitinib patients: 18 PR, 2 SD -6 erlotinib patients: 5 PR, 1 SD Authors' conclusions: -conclude TKI may have activity and should be considered as treatment of choice for this patient population
Long et al,[72] 2012	Dabrafenib in BRAF mutant (Val600Glu or Val600Lys) melanoma BM Multicenter, phase 2 trial Primary endpoint was intracranial response Patient population: 172 patients with BRAF mutant melanoma with $\geq$ asymptomatic BM 89 cohort A: no prior local therapy 83 cohort B: progressive BM after prior local therapy Treatment regimen: Dabrafenib 150 mg BID until progression, death or adverse event	III	Results: -prospective without control group -Val600Glu subgroup: 29/74 in cohort A and 20/65 in cohort B had overall intracranial response Authors' conclusions: -dabrafenib had activity and acceptable toxicities in Val600Glu mutant melanoma BM patients

Author, Year	Study Description	Data Class	Conclusions
Fokas et al,[50] 2012	Analysis of HER2 status and treatment outcome in patients with BM due to breast cancer Retrospective Patient population: 94 patients with BM due to breast cancer Evaluated for outcomes based on receptor status, trastuzumab use, RPA class, etc. Treatment regimen: Multiple	III	Results: -retrospective, no control -trastuzumab therapy associated with longer OS -questionable inclusion in evidence table given lack of specific data in manuscript Authors' conclusions: -effect of trastuzumab on survival likely relates to improved systemic disease control
Falchook et al,[71] 2012	Dabrafenib in melanoma and other cancers Phase 1 trial to evaluate safety and determine MTD MTD used in phase 2 trial Patient population: 3 cohorts 1: metastatic melanoma 2: untreated melanoma BM (10 patients) 3: non-melanoma solid tumors Treatment regimen: Dabrafenib 150 mg BID	III	Results: -prospective, no control groups for BM patients, small number -dabrafenib 150 mg BID determined to be MTD -9/10 patients with untreated melanoma BM had observable radiographic response and median PFS was 4.2 months Authors' conclusions: -good activity in BM and additional studies warranted

Author, Year	Study Description	Data Class	Conclusions
Bartsch et al,[44] 2012	Anti-HER2 agents in patients with BM due to HER2+ breast cancer Retrospective single center Patient population: 80 patients with BM due to HER2+ breast cancer 43 received trastuzumab as part of therapy -28 trastuzumab ± chemotherapy -15 additional treatment with lapatinib Control group: 37 patients prior to 2003 when discontinuation of trastuzumab was recommended upon diagnosis of BM Treatment regimen: Specific dosing not stated	III	Results: -retrospective with control group -median OS 13 months for patients who received trastuzumab after diagnosis of BM -median OS 9 months in chemotherapy group and 3 months in RT alone group -median survival not reached in lapatinib group -addition of lapatinib increased OS compared to trastuzumab alone Authors' conclusions: -addition of lapatinib after diagnosis of BM may improve OS in this patient population
Porta et al,[56] 2011	Impact of EGFR mutation on response of patients with NSCLC BM to erlotinib Retrospective, single center Patient population: 69 patients with NSCLC BM -17 with EGFR mutation -52 with unknown EGFR status or known wild type EGFR Treatment regimen: All patients received erlotinib 150 mg daily 55 patients treated with WBRT prior to erlotinib	III	Results: -retrospective with control -response rate with EGFR mutation 82% -PFS for BM 11.7 months with EGFR mutation, 5.8 months for control -median OS 12.9 months with EGFR mutation vs 3.1 months for control patients Authors' conclusions: - erlotinib is active in EGFR mutant NSCLC BM

Author, Year	Study Description	Data Class	Conclusions
Metro et al,[43] 2011	Lapatinib and capecitabine for patients with HER2+ breast cancer with BM Single center case series Patient population: 81 patients treated with L + C; all had been previously treated with trastuzumab 30/81 patients with BM; 26/30 had prior cranial RT All patients had received prior taxane, an anthracycline and trastuzumab Treatment regimen: Lapatinib 1250 mg oral daily Capecitabine 1000 mg/m^2 BID daily for 14 days, then 7 days off	III	Results: -7/22 patients evaluable had PR, 6 had stable disease -median CNS PFS 5.6 months -at time of diagnosis of BM, patients treated with L + C had significantly longer OS than patients treated with trastuzumab only (27.9 vs 16.7 months) Authors' conclusions: -L + C has activity vs BM due to HER2+ breast cancer in L + C naïve patients -LC appears to have activity vs BM in this population; RCT warranted
Lin et al,[48] 2011	Randomized phase 2 study of lapatinib + capecitabine vs lapatinib + topotecan for HER2+ breast cancer BM Primary endpoint CNS response (>50% reduction in BM volume) Study closed after 22/110 patients enrolled due to toxicity and lack of efficacy in L + T group Randomized multi-center Patient population: 22 patients with new or progressive BM due to HER2+ breast cancer despite prior RT (WBRT or SRS) Treatment regimen: -L + C: lapatinib 1250 mg PO QD and capecitabine 2000 mg/m2 PO divided into 2 doses per day on days 1-14 of 21-day cycle -L + T: lapatinib 1250 mg PO QD and topotecan 3.2 mg/m^2 on days 1, 8 and 15 of 28 day cycle	III	Results: -randomized with control but trial only 20% completed at time of halting -response rate in L + C arm 38% -no responses in L + T arm -seems that lapatinib not active given lack of activity in L + T arm Authors' conclusions: -L + C may have activity

Author, Year	Study Description	Data Class	Conclusions
Grommes et al,[55] 2011	Weekly high-dose erlotinib for BM due to EGFR mutant NSCLC High dose erlotinib previously shown to have good CSF penetration Retrospective review, single center Patient population: 9 patients who received high dose pulsatile erlotinib for CNS disease refractory to standard dose erlotinib or other EGFR TKI Treatment regimen: Monotherapy Erlotinib 1500 mg once per week	III	Results: -retrospective, no control -median brain PFS 2.7 months -PR in 6 patients -median OS 12 months Authors' conclusions: -erlotinib has activity vs NSCLC BM and warrants further trial
Chargari et al,[49] 2011	WBRT + trastuzumab for treatment of HER2+ breast cancer BM Retrospective, single institution Patient population: 31 patients with HER2+ breast cancer BM Treatment regimen: Trastuzumab 2 mg/kg weekly (n= 17) or 6 mg/kg every 21 days (n= 14) WBRT 30 Gy in 10 fractions (n= 26) or other fractionation schedule based on patient preference	III	Results: -retrospective, no control -6 patients with CR, 17 with PR -median OS 18 months -median brain PFS 10.5 months -low toxicity -difficult to determine how to attribute effects given concurrence of WBRT and trastuzumab Authors' conclusions: -additional studies needed

Author, Year	Study Description	Data Class	Conclusions
Sutherland et al,[42] 2010	Treatment of HER2+ breast cancer with lapatinib and capecitabine as part of lapatinib expanded access program -Evaluation of subset of total patient population which had BM -Safety and PFS, as well as efficacy with BM -Multi-center Patient population: 356 patients previously received trastuzumab, anthracycline and taxane; all HER2+ 34 patients with BM Patients not candidates for other lapatinib trials Treatment regimen: Capecitabine 2000 mg/m^2 daily in 2 doses for 14 days, then 7 days rest Lapatinib 1250 mg daily	III	Results: -retrospective analysis of prospective case series without control -response rate among BM patients 21%; median PFS 22 weeks Authors' conclusions: -response rates among this heavily treated population compare favorably with prior trials -lapatanib + capecitabine is an alternative for patients with treatment refractory metastatic breast cancer with BM
De Braganca et al,[66] 2010	Bevacizumab for active NSCLC BM -Assessment of efficacy and safety -Retrospective single center Patient population: -6 patients with treatment naïve (n= 1) or progressive after treatment (n= 5) NSCLC BM Treatment regimen: Bevacizumab alone or in combination with cytotoxic therapies Bevacizumab dose not given	III	Results: -retrospective, no control, small number -2 patients with PR -median PFS 4.7 months -median OS 14.1 months -generally, neurologic symptoms improved and steroid dose decreased Authors' conclusions: -bevacizumab may be safe and have activity but additional studies warranted

Author, Year	Study Description	Data Class	Conclusions
Lind et al,[54] 2009	Phase 1 study of WBRT + erlotinib for multiple NSCLC BM -Primary goal to evaluate safety/toxicity -Single center Patient population: 11 patients with NSCLC multiple BM who were not candidates for surgery or SRS Treatment regimen: Erlotinib started 1 week prior and continued through WBRT WBRT 30 Gy in 10 fractions 4 in cohort 1: erlotinib 100 mg/day 7 in cohort 2: erlotinib 150 mg/day Maintenance erlotinib 150 mg/day	III	Results: -case series, no control -no significant toxicity in cohort 1 -2 patients in cohort 2 died due to erlotinib related interstitial lung disease -median OS 133 days -median PFS 142 days -3 month MRI: 5/7 PR, 2/7 stable disease Authors' conclusions: -treatment strategy is safe and their data suggest good activity
Lin et al,[46] 2009	Phase 2 study of lapatinib in patients with BM due to HER2+ breast cancer -Study performed to further evaluate prior results from smaller phase 2 study that indicated activity of lapatinib for CNS metastases due to HER2+ breast cancer -Study expanded to allow patients with progressive BM on lapatinib to receive combination lapatinib + capecitabine -Multicenter Patient population: 242 patients with progressive BM due to HER2+ breast cancer after prior RT and trastuzumab Treatment regimen: Lapatinib 750 mg BID Capecitabine 1000 mg/m^2 BID for days 1-14 of 21-day cycle	III	Results: -large case series without control population; prospective -CNS response to lapatinib seen in 6% of patients -20% CNS response among the 50 patients who received lapatenib + capecitabine Authors' conclusions: -confirms modest activity of lapatinib vs HER2+ breast cancer BM which are progressive after RT and trastuzumab -lapatinib has possible modest activity as monotherapy

Author, Year	Study Description	Data Class	Conclusions
Lin et al,[45] 2008	Phase 2 trial of lapatinib for HER2+ breast cancer BM -Evaluate safety and efficacy -Multi-center Patient population: 39 patients with HER2+ breast cancer with progressive BM and prior trastuzumab therapy All developed BM while receiving trastuzumab 37 had progressed after RT Treatment regimen: Lapatinib 750 mg BID	III	Results: -case series, no control -1 patient had partial response Authors' conclusions: -no evidence of activity by their criteria, but that analysis of volume of BM reveals some activity that warrants further study -data do not support lapatinib as monotherapy for progressive BM in patients with HER2+ breast cancer after prior trastuzumab

BID, twice daily; BM, Brain metastases; CNS, Central nervous system; CR, Complete response; CSF, Cerebrospinal fluid; EGFR, Epidermal growth factor receptor; Gy, Gray; KPS, Karnofsky performance status; MTD, Maximum tolerated dose; NSCLC, Non-small cell lung cancer; ORR, Objective response rate; OS, Overall survival; PFS, Progression-free survival; PR, Partial response; QoL, Quality of life; RCC, Renal cell carcinoma; RCT, Randomized controlled trial; RT, Radiotherapy; SRS, Stereotactic radiosurgery; WBRT, Whole brain radiation therapy.

APPENDIX A. Brain Metastasis Root Search

PUBMED (NLM), searched on March 7, 2016:
Step 1: brain neoplasms [MeSH]
Step 2: (brain[Title/Abstract] OR brainstem[Title/Abstract] OR intracranial[Title/Abstract]) AND (cancer*[Title/Abstract] OR tumor*[Title/Abstract] OR tumour*[Title/Abstract] OR neoplasm*[Title/Abstract])
Step 3: Step 1 OR Step 2
Step 4: Neoplasm [MeSH] OR Metastasis [MeSH]
Step 5: brain* [TIAB] OR brainstem* [TIAB] OR intracranial [TIAB] AND metastas* [TIAB]
Step 6: Step 4 OR Step 5
Step 7: Step 3 and Step 6
Step 8: brain neoplasms/secondary [MeSH]
Step 9: Step 7 OR step 8
Step 10: Step 9 AND English [Lang]
Step 11: Step 10 AND ("2008/01/09"[PDAT] : "2015/31/12"[PDAT]
Total: 16,827 Results
COCHRANE, searched on March 7, 2016:
Step 1: MeSH descriptor: [brain neoplasms] explode all trees
Step 2: ((brain or brainstem or intracranial) NEAR/3 (cancer* or tumor* or tumour* or neoplasm*)):ti,ab,kw
Step 3: Step 1 OR Step 2
Step 4: MeSH descriptor: [neoplasm metastasis] explode all trees
Step 5: ((brain or brainstem or intracranial) NEAR/3 (metastas*)):ti,ab,kw
Step 6: Step 4 or Step 5
Step 7: Step 3 and Step 6

Step 8: MeSH descriptor: [Brain neoplasms/secondary]
Step 9: Step 7 or Step 8
Total: 396 Results
Summary of Primary Root Search Combined from 2 database searches, total of 16,851 candidate articles

HIFU

PubMed Search HIFU

1. Root brain metastasis search
2. High intensity focused ultrasound ablation [Mesh]
3. (ultrasound*) AND (intens* OR ablat* OR therapy* OR focus*) [TIAB]
4. #2 OR #3
5. #1 AND #4

N = 46

Cochrane CENTRAL Search HIFU

1. Brain metastasis root search
2. MeSH descriptor: [High-intensity focused ultrasound ablation] explode all trees
3. ((ultrasound*) NEAR/3 (intens* or ablat* or therap* or focus*)):ti,ab,kw
4. #2 OR #3
5. #1 AND #4

N = 0

Immune Therapy

PubMed Search for Immune Therapy

1. Root brain metastasis search
2. Immunomodulation OR immunomodulators OR immunomodulatory therapy OR immunotherapy [Mesh]
3. Immune* AND (therap* OR modu* OR drug* OR agent* or med*) [TIAB]
4. #2 OR #3
5. #1 AND #4

N = 364

Cochrane CENTRAL Search for Immune Therapy

1. Brain metastasis root search

2. MeSH descriptor: [immunomodulation] explode all trees
3. ((immune*) NEAR/3 (mod* or agent* or drug* or med* OR therap*)):ti,ab,kw
4. #2 OR #3
5. #1 AND #4

N = 6

LITT

PubMed Search for LITT

1. Root brain metastasis search
2. Laser therapy OR laser ablation [Mesh]
3. laser AND (therap* OR ablat* OR therm*) [TIAB]
4. #2 OR #3
5. #1 AND #4

N = 50

Cochrane CENTRAL Search for LITT

1. Brain metastasis root search
2. MeSH descriptor: [Laser therapy] explode all trees
3. ((laser or therm* or interstitial) NEAR/3 (ablat* OR therap*)):ti,ab,kw
4. #2 OR #3
5. #1 AND #4

N = 2

Local Therapy

PubMed Search for Local Therapy (2008 to present)

1. Root brain metastasis search
2. Drug implants or drug delivery system or infusion, intralesional [Mesh]
3. (interstitial or local or wafer) and (chemo* or Carmustine or convect* or therap*)[TIAB]
4. #2 OR #3
5. #1 AND #4

N = 567

Cochrane CENTRAL Search for Local Therapy

1. Brain metastasis root search
2. MeSH descriptor: [drug implants] explode all trees
3. ((interstitial or local or wafer or deliver*) and (chemo* or Carmustine or convect* or therap*)):ti,ab,kw
4. #2 OR #3
5. #1 AND #4

N = 20

Molecular Therapy

PubMed Search for Molecular Therapy

1. Root brain metastasis search
2. Targeted molecular therapy [Mesh]
3. (Molec*) AND (therap* OR drug* OR agent* OR target*) [TIAB]
4. #2 OR #3
5. #1 AND #4

N = 532

Cochrane CENTRAL Search for Molecular Therapy

1. Brain metastasis root search
2. MeSH descriptor: [molecular targeted therapy] explode all trees
3. ((mol* or target*) NEAR/3 (drug* or agent* or therap*)):ti,ab,kw
4. #2 OR #3
5. #1 AND #4

N = 5

Radiation Sensitizers

PubMed Search for Radiation Sensitizers

1. Root brain metastasis search
2. Rdiation sensitizers [Mesh]
3. (radiat* or radio* or radi*) AND (sens* or sensit*) [TIAB]
4. #2 OR #3
5. #1 AND #4

N = 148

Cochrane CENTRAL Search for Radiation Sensitizers

1. Brain metastasis root search
2. MeSH descriptor: [radiation sensitizer] explode all trees
3. ((rad*) NEAR/3 (sens*)):ti,ab,kw
4. ((radiat* or radio* or radi*) near/3 (sens* or sensit*)):ti,ab,kw
5. #2 or #3 or #4
6. #1 AND #5

N = 10

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