ASCO special articles

Management of Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: ASCO Guideline Update

Naren Ramakrishna, MD, PhD[1]; Carey K. Anders, MD[2]; Nancy U. Lin, MD[3]; Aki Morikawa, MD, PhD[4]; Sarah Temin, MSPH[5]; Sarat Chandarlapaty, MD, PhD[6]; Jennie R. Crews, MD[7]; Nancy E. Davidson, MD[8]; Maria Alice B. Franzoi, MD[9]; Jeffrey J. Kirshner, MD[10]; Ian E. Krop, MD, PhD[3]; Debra A. Patt, MD, MPH, MBA[11]; Jane Perlmutter, PhD[12]; and Sharon H. Giordano, MD, MPH[13]

abstract

PURPOSE To provide updated evidence- and consensus-based guideline recommendations to practicing oncologists and others on the management of brain metastases for patients with human epidermal growth factor receptor 2 (HER2)–positive advanced breast cancer up to 2021.

METHODS An Expert Panel conducted a targeted systematic literature review (for both systemic therapy for non-CNS metastases and for CNS metastases of HER2+ guideline updates) that identified 545 articles. Outcomes of interest included overall survival, progression-free survival, and adverse events.

RESULTS Of the 545 publications identified and reviewed, six on systemic therapy were identified to form the evidentiary basis for the systemic therapy for CNS metastases guideline recommendations.

RECOMMENDATIONS Patients with brain metastases should receive appropriate local therapy and systemic therapy, if indicated. Local therapies include surgery, whole-brain radiotherapy, and stereotactic radiosurgery. Memantine and hippocampal avoidance should be added to whole-brain radiotherapy when possible. Treatments depend on factors such as patient prognosis, presence of symptoms, resectability, number and size of metastases, prior therapy, and whether metastases are diffuse. Other options include systemic therapy, best supportive care, enrollment onto a clinical trial, and/or palliative care. There are insufficient data to recommend for or against performing routine magnetic resonance imaging to screen for brain metastases; clinicians should have a low threshold for magnetic resonance imaging of the brain because of the high incidence of brain metastases among patients with HER2-positive advanced breast cancer.

Additional information is available at www.asco.org/breast-cancer-guidelines.

ASSOCIATED CONTENT

Appendix

Data Supplement

Author affiliations and support information (if applicable) appear at the end of this article.

Accepted on April 5, 2022 and published at ascopubs.org/journal/jco on May 31, 2022: DOI https://doi.org/10.1200/JCO.22.00520

Evidence Based Medicine Committee approval: February 15, 2022

INTRODUCTION

Approximately 15%-20% of patients with breast cancer have tumors that overexpress the human epidermal growth factor receptor 2 (HER2) protein.[1] With the development of HER2-targeted therapies, survival has improved for patients with both early-stage and metastatic breast cancers. HER2 positivity is a known risk factor for the development of brain metastases. Although only a small fraction of patients (1%-3%) presenting with early-stage breast cancer will relapse with the brain as the first site of recurrence, up to 5% of patients with residual disease after neoadjuvant therapy will present with CNS as the first site of relapse, and brain metastases are increasingly common in patients with HER2-positive metastatic breast cancer, with up to half of patients experiencing brain metastases over time. Notably, brain metastases seem to occur in a continuous fashion, with continued events even after many years from initial metastatic diagnosis.

Historically, survival of patients diagnosed with brain metastases has been quite poor. However, in the case of HER2-positive breast cancer, as systemic therapies for control of extracranial disease improve, an increasing number of patients are experiencing extended survival. For example, on the basis of a multi-institutional retrospective database of patients treated in the United States, the median survival for a patient with estrogen receptor (ER)–positive, HER2-positive breast cancer and good performance status, even with multiple brain metastases and coexisting extracranial metastases, has been estimated at approximately 3 years, and this experience has been borne out in other retrospective studies.[2] Therefore, there is an

THE BOTTOM LINE

Management of Advanced Human Epidermal Growth Factor Receptor 2-Positive Breast Cancer and Brain Metastases: ASCO Guideline Update

Target Population

Individuals with advanced human epidermal growth factor receptor (HER2)–positive breast cancer and brain metastases.

Target Audience

Medical oncologists, radiation oncologists, neurosurgeons, oncology nurses, patients, and caregivers.

Methods

An Expert Panel was convened to develop clinical practice guideline recommendations.

Key Recommendations (Fig 1)

- For patients with a favorable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, stereotactic radiosurgery (SRS) alone, whole-brain radiotherapy (WBRT) plus memantine (WB-M) and hippocampal avoidance (HA; ± SRS), hypofractionated stereotactic radiotherapy, and discussion of systemic therapy in select patients with asymptomatic CNS metastases depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2-4 months may be used to monitor for local recurrence or new brain disease.

- For patients with a favorable prognosis for survival and limited (two to four) metastases, treatment options include resection for large symptomatic lesion(s) plus postoperative radiotherapy, SRS for additional smaller lesions, SRS (± WB-M and HA), hypofractionated stereotactic radiotherapy, or WB-M and HA (± SRS) for inoperable metastases > 3-4 cm.

- For metastases < 3-4 cm, treatment options include resection with postoperative radiotherapy, SRS alone, WB-M and HA (± SRS), hypofractionated (SRS), and discussion of systemic therapy in select patients with asymptomatic CNS metastases. In both cases, available options depend on resectability and symptoms.

- For patients with diffuse disease and/or extensive metastases and a more favorable prognosis or those with symptomatic leptomeningeal metastasis in the brain, SRS or WB-M and HA may be offered.

- For patients with symptomatic leptomeningeal metastasis in the brain, WBRT plus memantine may be offered.

- For patients with poor prognosis, options include WB-M and HA, best supportive care, and/or palliative care.

- For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WB-M and WB-M, a trial of systemic therapy, enrollment onto a clinical trial, and/or additional palliative options depending on initial treatment.

- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched from their current HER2-targeted therapy regimen.

- For patients whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer.

- The HER2CLIMB regimen of tucatinib plus capecitabine plus trastuzumab may be offered to patients with HER2-positive metastatic breast cancer who have brain metastases without symptomatic mass effect and whose disease has progressed on ≥ one HER2-directed therapy for metastatic disease. If these agents are used, local therapy may be delayed until evidence of intracranial progression.

- The HER2CLIMB regimen of tucatinib plus capecitabine plus trastuzumab may be offered to patients with stable brain metastases after local therapy or intracranial disease progression, in addition to the option in the systemic therapy guideline update's recommendation of trastuzumab deruxtecan in second-line.

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- If a patient does not have a known history or symptoms of brain metastases, there are insufficient data to recommend for or against performing routine surveillance with brain magnetic resonance imaging.
- Clinicians should have a low threshold for performing diagnostic brain magnetic resonance imaging testing in the setting of any neurologic symptoms suggestive of brain involvement.

Additional Resources

Definitions for the quality of the evidence and strength of recommendation ratings are available in Appendix Table A3 (online only). More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. The Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the methods used to develop this guideline. Patient information is available at www.cancer.net.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care, and that all patients should have the opportunity to participate.

increasing need to optimize initial treatments for brain metastases as well as to develop strategies to manage subsequent intracranial progression events. This guideline addresses what is known about the management of patients with HER2-positive advanced breast cancer and brain metastases. This guideline will not provide comprehensive recommendations for the management of non-CNS disease in patients with HER2-positive advanced breast cancer or provide guidance on HER2 testing, other than noting that quality HER2 testing is required for appropriate identification and management of patients with HER2-positive disease. The ASCO clinical practice guideline on systemic therapy for patients with advanced HER2-positive breast cancer accompanies this article,[3] and the ASCO-College of American Pathologists issued a joint clinical practice guideline on HER2 testing in breast cancer.[4]

This guideline covers the management of patients with HER2-positive breast cancer and brain metastases. The guideline is meant to provide recommendations specific to patients with HER2-positive disease, in whom the overall prognosis after diagnosis of brain metastases and treatment can be more favorable. These recommendations supplement existing guidelines that address brain metastases for patients with other types of cancer[5] and the companion recommendations for systemic therapy.[3]

GUIDELINE QUESTIONS

This clinical practice guideline addresses one overarching question and four subquestions: Overall, what is the appropriate course of treatment for patients with HER2-positive advanced breast cancer and brain metastases? Additionally, (1) Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer? (2) How should systemic therapy be managed in patients with HER2-positive brain metastases (including management of systemic therapy when the brain is the only site of progression versus when progression occurs in both the brain and elsewhere)? (3) Is there a role for systemic therapy specifically to treat brain metastases in HER2-positive breast cancer? and (4) Should patients with HER2-positive breast cancer be screened for development of brain metastases?

METHODS

Guideline Development Process

ASCO convened a multidisciplinary Expert Panel, which included a patient representative and an ASCO guidelines staff member with health research methodology expertise to update this systematic review-based guideline product on the treatment of patients with advanced HER2-positive breast cancer and CNS metastases (Appendix Table A1, online only). The recommendations were developed by a multidisciplinary group of experts using evidence from randomized clinical trials, observational studies, and clinical experience as a guide. The Expert Panel and a brain metastases writing group (subgroup of the Expert Panel) met via webinar and corresponded through e-mail. Based upon the consideration of the evidence, the authors were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The guideline recommendations were sent for an open comment period of two weeks allowing the public to review and comment on the recommendations after submitting a confidentiality agreement. These comments were taken into consideration while finalizing the recommendations. The members of the Expert Panel were responsible for reviewing and approving the penultimate version of the guideline, which was then circulated for external review, and submitted to the *Journal of Clinical Oncology* for editorial review and consideration for publication. All ASCO guidelines are ultimately reviewed and

approved by the Expert Panel and the ASCO Evidence Based Medicine Committee before publication. All funding for the administration of the project was provided by ASCO. The Expert Panel did not conduct a systematic review because the prior guideline was formal consensus-based. A literature search for evidence on systemic therapy for brain metastases was conducted along with the other systemic therapy guideline's search. The recommendations were developed by using a systematic review of the systemic therapy for brain metastases portions and informal consensus for the local therapy portions. The systematic review of systemic therapy included searches on MEDLINE from August 2016 through April 2021 (to update searches from the 2018 update) of phase II and III randomized clinical trials and clinical experience. Articles were selected for inclusion in the systematic review on the basis of the following criteria:

- Population: HER2-positive advanced breast cancer and central nervous system metastases
- Fully published English-language reports of phase II or III randomized clinical trials, rigorously conducted systematic reviews, or meta-analyses.
- Trials comparing a targeted agent (± chemotherapy and ± endocrine therapy) with another treatment regimen, placebo, or observation.

Articles were excluded from the systematic review if they were (1) meeting abstracts; (2) editorials, commentaries, letters, news articles, case reports, and narrative reviews; and (3) published in a non-English language. Evidence supporting unchanged recommendations is reviewed in the previous guideline publications.[1]

Quality of the evidence for each outcome was assessed using the Cochrane Risk of Bias tool and elements of the GRADE quality assessment and recommendations development process (for updated recommendations) or the ASCO method of quality assessment and recommendations development process (for previously developed recommendations).[6,7] GRADE quality assessment labels (ie, high, moderate, low, and very low) or ASCO labels (high, intermediate, low, and insufficient) were assigned for each outcome by the project methodologist in collaboration with the Expert Panel cochairs and reviewed by the full Expert Panel.

ASCO guidelines staff updated the literature search that was conducted to inform its recommendations on Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases. The ASCO Guidelines Methodology Manual (available at www.asco.org/guideline-methodology) provides additional information about the guideline update process. This is the most recent information as of the publication date. The ASCO Expert Panel and guidelines staff will work with cochairs to keep abreast of any substantive updates to the guideline. On the basis of formal review of the emerging literature, ASCO will determine the need to update.

Guideline Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon as being complete or accurate, nor should it be considered as inclusive of all proper treatments or methods of care or as a statement of the standard of care. With the rapid development of scientific knowledge, new evidence may emerge between the time information is developed and when it is published or read. The information is not continually updated and may not reflect the most recent evidence. The information addresses only the topics specifically identified therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations specify the level of confidence that the recommendation reflects the net effect of a given course of action. The use of words like "must," "must not," "should," and "should not" indicates that a course of action is recommended or not recommended for either most or many patients, but there is latitude for the treating physician to select other courses of action in individual cases. In all cases, the selected course of action should be considered by the treating provider in the context of treating the individual patient. Use of the information is voluntary. ASCO does not endorse third-party drugs, devices, services, or therapies used to diagnose, treat, monitor, manage, or alleviate health conditions. Any use of a brand or trade name is for identification purposes only. ASCO provides this information on an "as is" basis and makes no warranty, express or implied, regarding the information. ASCO specifically disclaims any warranties of merchantability or fitness for a particular use or purpose. ASCO assumes no responsibility for any injury or damage to persons or property arising out of or related to any use of this information, or for any errors or omissions.

Guideline and Conflicts of Interest

The Expert Panel was assembled in accordance with ASCO's Conflict of Interest Policy Implementation for Clinical Practice Guidelines ("Policy," found at https://www.asco.org/guideline-methodology). All members of the Expert Panel completed ASCO's disclosure form, which requires disclosure of financial and other interests, including relationships with commercial entities that are reasonably likely to experience direct regulatory or commercial impact as a result of promulgation of the guideline. Categories for disclosure include employment; leadership; stock or other ownership; honoraria, consulting or advisory role; speaker's bureau; research funding; patents, royalties, other intellectual property; expert testimony; travel, accommodations, expenses; and other relationships. In

accordance with the Policy, the majority of the members of the Expert Panel did not disclose any relationships constituting a conflict under the Policy.

BACKGROUND

- Systemic therapy: Interventions for systemic therapy for patients with HER2-positive advanced breast cancer, including patients with brain metastases, were included in the systematic review for the systemic guideline
- Radiation therapy and surgery: The Expert Panel did not conduct a systematic review because the prior guideline was formal consensus-based. However, ASCO conducted a separate systematic review for a separate guideline that was available to inform this HER2-positive specific guideline.[5]

The data cited for the local therapy section were not systematically collected, nor were they considered sufficiently specific to patients with HER2-positive disease to inform evidence-based recommendations; however, they were used to help members form opinions.

This section provides background on the recommendations on the management of patients with brain metastases (Appendix Table A2, online only). Brain metastases are common in patients with advanced HER2-positive breast cancer, with up to half of patients (40%-50%) experiencing brain relapse before death.[6-9] As of the original 2014 production of this guideline, there were not many other published guidelines on the treatment of patients with HER2-positive breast cancer and brain metastases. A recent ASCO guideline on all CNS metastases includes patients with HER2-positive cancer.[5] Existing brain metastasis treatment guidelines, such as those developed by the National Comprehensive Cancer Network, are not disease-specific.[8] General guidelines for treatment may be divided by prognosis of patients and extent of brain metastatic disease. Patients with favorable prognoses are those with good performance status and effective systemic therapy options. The criteria may include Karnofsky performance status (KPS) > 70, controlled extracranial disease, and/or whether good salvage systemic therapy options for extracranial disease are available.[2] Sperduto et al[2] found that the worst survival in patients with breast cancer brain metastases were those with KPS ≤ 60, age ≤ 60 years, > 1 brain metastasis, active extracranial disease, and triple-negative histology. In some studies, although HER2-positive status was associated with relatively good survival among patients with breast cancer brain metastases, there was a shorter interval from diagnosis of primary breast cancer to the development of brain metastases in both patients with HER2-positive breast cancer and those with triple-negative breast cancer.

A majority of the available high-level data on the management of patients with brain metastases are not specific to patients with breast cancer. Studies often pool patients with breast cancer of all subtypes together with patients with other tumor types (eg, lung cancer). Data specific to patients with breast cancer are often from single-arm or observational studies. In addition, several of these studies were conducted in the pre–HER2-targeted therapy era. Approximately 5% of patients with advanced HER2-positive breast cancer and brain metastases have leptomeningeal metastases[10] (see https://www.cancer.net/cancer-types/brain-tumor/statistics), but this guideline does not comprehensively review treatment of patients with leptomeningeal metastases.

Because the ASCO guideline a priori criteria to include evidence in this guideline were not met for local therapy and the original 2014 recommendations were developed with formal expert consensus, the updated recommendations on patients with HER2-positive breast cancer with brain metastases were modified by informal expert consensus. As part of the development of various types of ASCO recommendations (eg, formal consensus and evidence-based), panels of experts rate the overall quality of the evidence and the strength of each recommendation (Appendix Table A3, online only). Using these ratings, the Expert Panel assigned a recommendation strength of weak for most recommendations (except where specifically noted). This connotes that there is some confidence that the recommendation offers the best current guidance for practice.

Local Therapy

The principal local therapies for brain metastatic disease are surgery, whole-brain radiotherapy (WBRT), and stereotactic radiosurgery (SRS).

- WBRT has played an important role in the palliative radiotherapy of patients with brain metastases for more than five decades but is associated with concerning short- and long-term complications including neurocognitive decline and fatigue.
- Memantine given concurrently and for six months following WBRT was shown to delay time to cognitive decline following WBRT in a randomized, double-blind, placebo-controlled trial.[9]
- In a subsequent phase III randomized trial, patients treated with WBRT with hippocampal avoidance (HA) combined with memantine showed improved cognitive preservation versus those treated with WBRT plus memantine (WB-M).[11]
- Given these data, when WBRT is used, clinicians should add memantine (WB-M) and, in addition, HA if no metastases are present within 5 mm of the hippocampus.[5,9,11]
- The utilization of WBRT (plus memantine and hippocampal avoidance [WB-M + HA]) and SRS has continued to evolve with a disease-specific and patient-specific approach.
- Since the previous update, emerging evidence presents a new option to defer local therapy for a subset of

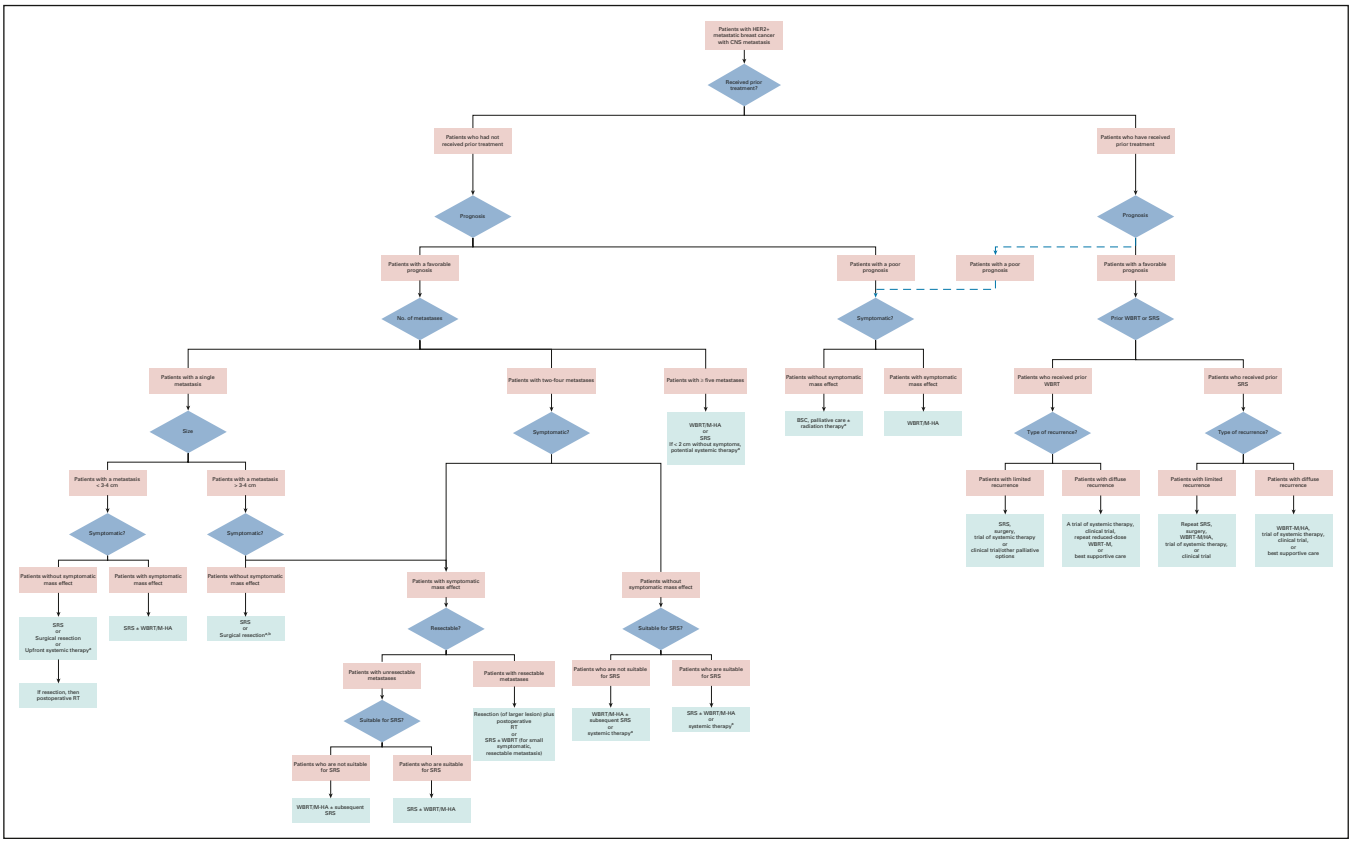

FIG 1. Algorithm. [a]After consultation with a multidisciplinary team. [b]Upfront systemic therapy can be discussed for select cases. BSC, best supportive care; HA, hippocampal avoidance; HER2+, human epidermal growth factor receptor 2–positive; M, memantine; SRS, stereotactic radiosurgery; RT, radiotherapy; WBRT, whole-brain radiotherapy.

the target population. The guideline discusses this evidence under Systemic Therapy.

- A particularly important consideration for patients with HER2-positive breast cancer and brain metastases is the role of WB-M + HA versus surgery, SRS, and hypofractionated stereotactic radiotherapy (HSRT), in the management of limited (defined as two-four metastases) brain metastatic disease.
- There are no head-to-head trials comparing efficacy and toxicity of local therapy alone (surgery, SRS, and HSRT) versus WB-M + HA ± SRS.

Systemic Therapies

- Since ASCO last updated this guideline, there has been more research on systemic therapy for patients with HER2-positive metastatic breast cancer with CNS metastases (eg, the HER2CLIMB study[12]).

METHODS AND RESULTS

As part of updating the systemic therapy guideline, evidence was found regarding the role of systemic therapy and CNS.[3] Four studies (in five publications)[12-16] ultimately formed the evidence base for the CNS systemic therapy recommendations. The identified trials were published between 2016 and 2020. Readers are referred to the Giordano et al[3] guideline for further methods and results. Characteristics of the studies are provided in Table 1. Patient characteristics are provided in Table 2. The results are provided in Tables 3-7.

Study design aspects related to individual study quality, quality of evidence, strength of recommendations, and risk of bias were assessed. Refer to the Methodology Manual for more information and for definitions of ratings for overall potential risk of bias.

The 2014 guideline described the LANDSCAPE trial and stated at the time, the overall impact on quality of life of this approach remains to be determined; however, further study is required before this approach can be considered a standard approach in patients with HER2-positive brain metastases.[1]

If patients have asymptomatic, low-volume brain metastases and have not received radiation therapy, upfront therapy with a variety of systemic therapy options is an option, although radiation therapy in this setting is still the standard option.

Treatment of Intracranial Progression After Initial Therapy

There are no high-level, randomized data to guide the choice of treatment in patients whose disease has progressed in the

TABLE 1. Study Characteristics

Reference	Tx Line	Arm 1, Intervention(s)	Arm 2, Intervention(s)	Arm 3, Intervention(s)	Inclusion Criteria	Exclusion Criteria	Primary Outcome	Secondary Outcome	No. of Patients Analyzed	No. of Patients Analyzed, Safety
Awada et al[13]	First-line	Neratinib plus paclitaxel	Trastuzumab plus paclitaxel		Adults Confirmed recurrent/ metastatic FISH > 2.2 or CISH or IHC 2+ or 3+ (local or central) Regarding CNS metastases: asymptomatic and treated—newly diagnosed, history of mets, or spinal compression	Prior treatment (except [neo] adjuvant trastuzumab ± lapatinib)	PFS	AEs response rate DoR other: time to symptomatic or progressive CNS mets	Arm 1: 242 Arm 2: 237' Overall: 479	Arm 1: 240 Arm 2: 234 Overall: 474
Montemurro et al[17]	Second-line > Second-line	Trastuzumab emtansine (T-DM1) alone	Other		Prior HER2+ targeted tx plus chemotherapy DP during tx, after tx, or within 6 months of adjuvant tx Untreated, asymptomatic CNS mets or controlled CNS disease tx with RT > 14 days	Prior T-DM1 tx Grade ≥ 3 peripheral neuropathy Symptomatic CNS mets	AEs NOTE: efficacy in subgroup	PFS OS	2003	2002
Lin et al[15]	> Second-line	Tucatinib plus trastuzumab plus chemotherapy	Placebo plus trastuzumab plus chemotherapy		Adults HER2+ IHC, ISH, FISH, central laboratory Prior treatment: trastuzumab, pertuzumab, T-DM1 ECOG PS 0-1 CNS mets (except immediate local intervention needed)	Leptomeningeal mets	Other: Disease response and progression in brain; intracranial response		Arm 1: 198 Arm 2: 93 Overall: 291	NR
Murthy et al[12]	> Second-line	Tucatinib plus trastuzumab plus chemotherapy	Placebo plus trastuzumab plus chemotherapy		Adults HER2+ IHC, ISH, FISH, central laboratory Prior treatment: trastuzumab, pertuzumab, T-DM1 ECOG 0-1 CNS mets (except immediate local intervention needed)	Prior capecitabine or HER2-targeted TKI (except lapatinib > 12 months	PFS: primary end point analysis population	PFS: in % of those with brain metastases in total population OS: total population AEs Response rate	Arm 1: 320 Arm 2: 160 Overall: 480 Note: Brain mets 148 *v* 71	Arm 1: 404 Arm 2: 197 Overall: 601
Saura et al[16]	> Second-line	Neratinib plus chemotherapy	Lapatinib plus chemotherapy		Adults ECOG PS ≤ 1 HER2+, central laboratory ≥ 2 prior HER2-directed tx CNS mets if asymptomatic		PFS OS	AEs QOL response rate Other: time to intervention for CNS, DoR	Arm 1: 307 Arm 2: 314 Overall: 621	Arm 1: 303 Arm 2: 311 Overall: 614

Abbreviations: AE, adverse event; BC, breast cancer; CISH, chromogenic in situ hybridization; DoR, duration of response; DP, disease progression; ECOG PS, Eastern Cooperative Oncology Group performance status; ER, estrogen receptor; FISH, fluorescence in situ hybridization; HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridization; mets, metastases; NR, not reported; OS, overall survival; PD-1, programmed cell death-1; PFS, progression-free survival; QOL, quality of life; RT, radiation therapy; SD, stable disease; T-DM1, trastuzumab emtansine; TKI, tyrosine kinase inhibitor; Tx, treatment.

brain after initial therapy, and the impact on overall survival (OS) is unclear. Not surprisingly, disease burden, tumor subtype, and performance status influence survival after treatment for intracranial progression.

Because this guideline is intended to specifically cover patients with HER2-positive advanced breast cancer, the authors chose key areas that may be specific to these patients and do not intend these recommendations to comprehensively provide guidance for managing patients with all types of breast cancer or brain metastases. Other issues that are not addressed here further include radiation necrosis and supportive care for patients with brain metastases. A recent ASCO guideline[5] and other groups' guidelines address some of these issues more in-depth for patients with brain metastases, although not specifically for those with HER2-positive disease, including leptomeningeal metastases and/or supportive care for patients with brain metastases.

Assumptions underlying these recommendations include the fact that existing high-level evidence is not specific to patients with brain metastases who have HER2-positive metastatic breast cancer, and therefore, it is not possible to rate the aggregate evidence as high. In addition, the authors favor a team approach to the management of the patients described in this guideline. A team ideally includes radiation oncologists, neurosurgeons, neuroradiologists, and medical oncologists.

This guideline updates the first (formal) expert consensus-based recommendations on the management of patients with HER2-positive breast cancer and brain metastases. The Expert Panel suggests that future research in this patient population will further inform this area. The Data Supplement provides further information.

RECOMMENDATIONS

Please note: Modifications from 2014 recommendations appear in italic fonts.

The Expert Panel endorses the principle of multidisciplinary teams as described in another ASCO guideline's recommendations:

Recommendation 1.0

Multidisciplinary collaboration to formulate treatment and care plans and disease management for patients with HER2-positive metastatic breast cancer should be the standard of care (Type: Evidence based, benefits outweigh harms; Evidence quality: intermediate; Strength of recommendation: Strong).[19]

Overarching Clinical Question

What is the appropriate course of treatment for patients with HER2-positive advanced breast cancer and brain metastases?

Clinical Question 1

Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer?

Recommendation 2.1 (single brain metastasis, favorable prognosis). If a patient has a favorable prognosis for survival and a single brain metastasis, the patient should be evaluated by an experienced neurosurgeon for discussion of the option of surgical resection, particularly if the metastasis is > 3-4 cm and/or if there is evidence of symptomatic mass effect (Type: Formal and informal consensus; Evidence quality: Intermediate; Strength of recommendation: Strong) (no change).

Recommendation 2.2. If a patient has a favorable prognosis and a single brain metastasis < 3-4 cm without symptomatic mass effect, clinicians may offer either SRS or surgical resection, depending on the location and surgical accessibility of the tumor, need for tissue diagnosis, and other considerations, such as medical risk factors for surgery and patient preference (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Weak) (no change).

Recommendation 2.3. If a patient has a favorable prognosis and a single brain metastasis *< 2 cm* without symptomatic mass effect *and who has an option to proceed with HER2-directed therapy with known CNS activity*, then clinicians and patients may discuss options including *SRS* or *deferring local therapy with a multidisciplinary team (MDT)* (Type: Informal consensus; Evidence quality: Low; Strength of recommendation: Moderate).

Please see discussion of potential upfront systemic therapy in Clinical Question 2.

Recommendation 2.4. For most patients with brain metastases who undergo surgical resection, clinicians should recommend postoperative *radiotherapy (includes SRS, hypofractionated stereotactic radiotherapy (HSRT), and for large or multiple resection beds possibility of WB-M + HA)* to the resection bed to reduce the risk of local recurrence (Type: Formal and informal consensus; Evidence quality: Intermediate; Strength of recommendation: Weak) (no substantive change).

Recommendation 2.5. If a patient has a favorable prognosis and a single brain metastasis > 3-4 cm, which clinicians *and a MDT* deem unresectable and unsuitable for SRS, clinicians may discuss the options of HSRT or WB-*M + HA*. *MDTs should consult with patients in this situation* (Type: Formal and informal consensus; Evidence quality: Low; Strength of recommendation: Weak) (no substantive change).

Recommendation 2.6. After treatment, serial imaging every 2-4 months may be used to monitor for local and distant brain failure (also known as local recurrence or new brain disease) (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Weak) (no change).

Recommendation 4.2.2 provides a definition of favorable prognosis.

Recommendation 3.0. If a patient has a favorable prognosis and presents with multiple, but limited, metastases (defined as two-four lesions), treatment options depend on the size, resectability, and mass effect of the lesions.

Recommendation 3.1. In a patient who presents with limited metastases *[defined as two to four lesions]* suitable for SRS, clinicians may discuss SRS without WB-M + HA (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Weak) (no change).

Recommendation 3.2. In a patient with *symptomatic* lesions that are unresectable and unsuitable for SRS HSRT, clinicians may recommend WBRT *plus memantine and, if feasible, hippocampal avoidance* and may discuss SRS after WB-*M + HA* (Type: Formal and informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 3.3. *For patients with limited metastases < 2 cm and not associated with symptomatic mass effect, and who have an option to proceed with HER2-directed therapy with known CNS activity, then clinicians and patients may discuss deferring local therapy with a MDT* (Type: Informal consensus; Evidence quality: Low, Strength of recommendation: Moderate).

Please see discussion of potential upfront systemic therapy in Clinical Question 2.

Recommendation 3.4. In a patient who has a large (> 3-4 cm) lesion associated with symptomatic mass effect, clinicians may discuss surgical resection of the larger lesion, if the lesion is deemed resectable. The remaining lesions *and resection bed* may be treated with SRS, or HSRT with or without WB-*M + HA*. *Clinicians should also provide symptom management* (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Weak) (no substantive change).

Note that special circumstances include favorable prognosis and favorable risk-benefit ratio (ie, cases of symptomatic mass effect). Unsuitable refers to metastases > 3-4 cm or if SRS would result in excess dose to critical radiosensitive brain structures, such as the brainstem, optic nerves, and/or optic chiasm. The addition of WBRT to SRS in patients with one to four brain metastases is associated with decreased local recurrence or new brain disease but demonstrates no survival benefit.

Diffuse Disease or Extensive Metastases

Recommendation 4.1. If a patient has symptomatic brain leptomeningeal metastases, clinicians may recommend WBRT *plus memantine*. The management of leptomeningeal metastases is complex, and recommendations regarding intrathecal therapy and/or systemic therapy for leptomeningeal metastases are outside the scope of this practice guideline (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate) (no substantive change).

Note: The diagnosis and management of leptomeningeal disease is complex, and may include intrathecal and/or systemic therapy.

Recommendation 4.2.1. If a patient has a more favorable prognosis and presents with many diffuse and/or extensive brain metastases (≥ five metastases) without leptomeningeal disease, clinicians may recommend *SRS or* WB-*M + HA*. *For patients with metastases < 2 cm and not associated with symptomatic mass effect, and who have an option to proceed with HER2-directed therapy with known CNS activity, then clinicians and patients may discuss deferring local therapy with a MDT* (Type: Formal and informal consensus; Evidence quality: Low, Strength of recommendation: Moderate).

Recommendation 4.2.2. Patients with favorable prognoses are those with good performance status and effective systemic therapy options. The criteria may include KPS > 70, controlled extracranial disease, and/or whether good additional systemic therapy options for extracranial disease are available (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 5.0 (patients with poor prognosis). If a patient has brain metastases and a poor prognosis, clinicians should discuss the options of best supportive care and/or palliative care, which may or may not include radiation therapy, on a case-by-case basis (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Weak) (no change).

Recommendation 5.1. For a patient with symptomatic brain metastases and poor prognosis, WB-*M + HA* may be offered if there is a reasonable expectation of symptomatic improvement that outweighs the acute and subacute treatment-related toxicities, including fatigue and decline in neurocognitive function (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Weak) (no substantive change).

Recommendation 6.0 (patients with intracranial metastases, which progressed despite initial therapy). If a patient has intracranial metastases that progressed despite initial therapy, treatment options will depend on the patient's prior therapies, burden of disease, performance status, and overall prognosis (no substantive change).

Recommendation 6.1 (brain recurrence and prior WBRT; limited recurrence). For a patient with a favorable prognosis and limited recurrence after treatment with WBRT, clinicians may discuss SRS, surgery, systemic therapy, and/or additional palliative options.

For a patient with a favorable prognosis and limited recurrence after treatment with SRS, clinicians may discuss repeat SRS, surgery, WB-*M + HA*, systemic therapy, *and/or additional palliative options* (Type: Formal and informal consensus; Evidence quality: Low; Strength of recommendation: Moderate).

Recommendation 6.2 (diffuse recurrence). If a patient has diffuse recurrence after treatment with WBRT, clinicians

TABLE 2. Patient Characteristics

Reference	Tx Line	Arm 1, Intervention(s)	Arm 2, Intervention(s)	No. of Patients Analyzed	Age, median (range)	Disease Characteristics	Previous Treatment
Awada et al[13]	First-line	Neratinib plus paclitaxel	Trastuzumab plus paclitaxel	Arm 1: 242 (six with CNS mets at baseline) Arm 2: 237 (12 with CNS mets) Overall: 479 (28 with CNS mets)	54.5 (46-61) *v* 55.0 (47-62)	HER2+: 100% HER2+/ER+ and/or PR+: 52.9% *v* 51.9% HER2+/ER– and PR–: 47.1% *v* 48.1%	Prior (neo)adjuvant trastuzumab: 11.6% *v* 9.3% Prior (neo)adjuvant lapatinib: 0.8% *v* 0.8% Prior chemotherapy: 50.8% *v* 50.6%
Montemurro et al[17]	Second-line > second-line	Trastuzumab emtansine (T-DM1) alone	Other	Arm 1: 2,002 patients who received treatment, including 398 with baseline CNS mets, and 126/398 with measurable CNS mets	55.0 (26-88)	HER2+/ER+ and/or PR+: 61.8% HER2+/ER– and PR–: 37.7%	Prior number of treatment lines in the metastatic setting—0-1: 29.7%, 2: 22.3%, 3: 17.9%, 4+: 25.8%, Missing: 4.3%
Lin et al[15]	> Second-line	Tucatinib plus trastuzumab plus chemotherapy	Placebo plus trastuzumab plus chemotherapy Placebo	Arm 1: 198 Arm 2: 93 Overall: 291 Note: of total population	53 (22-75) *v* 52 (25-75)	HER2+/ER+ and/or PR+: 54.0% *v* 63.4% HER2+/ER– and PR–: 44.4% *v* 36.6%	Prior therapy for BMs—RT 70.7% *v* 68.8%; Surgery 16.7% *v* 14.0%
Murthy et al[12]	> Second-line	Tucatinib plus trastuzumab plus chemotherapy	Placebo plus trastuzumab plus chemotherapy	Arm 1: 320 (148 with CNS mets) Arm 2: 160 (71 with CNS mets) Overall: 480 (219 with CNS mets) Note: primary end point analysis population	54 *v* 54	HER2+: 100% HER2+/ER+ and/or PR+: 59.4% *v* 61.9% HER2+/ER– and PR–: 39.4% *v* 38.1%	Previous lines for metastatic cancer, median: 3 (1-14) *v* 3 (1-13)
Saura et al[16]	> Second-line	Neratinib plus chemotherapy	Lapatinib plus chemotherapy	Arm 1: 307 (51 with CNS mets Arm 2: 314 (50 with CNS mets) Overall: 621 (101 with CNS mets)	55 (47-63) *v* 54 (47-62)	HER2+/ER+ and/or PR+: 59.0% *v* 59.2% HER2+/ER–/PR–: 41.0% *v* 40.8%	Previous systemic anticancer therapy—neoadjuvant: 16.9% *v* 23.2%, adjuvant: 47.6% *v* 47.5%, metastatic: 100% *v* 99.7%

Abbreviations: BC, breast cancer; BM, brain metastasis; ER, estrogen receptor; HER2, human epidermal growth factor receptor 2; LTR, long-term responder; PR, progesterone receptor; RT, radiation therapy; T-DM1, trastuzumab emtansine; tx, treatment.

TABLE 3. Results Evidence Table

Reference	Tx Line	Arm 1, Intervention(s)	Arm 2, Intervention(s)	Arm 3, Intervention(s)	No. of Patients Analyzed	No. of Patients Analyzed, Safety	CNS Outcomes (1)	CNS Outcomes (2)	CNS Outcomes (3)
Murthy et al[12]	> Second-line	Trastuzumab plus chemotherapy Other: tucatinib	Trastuzumab plus chemotherapy Placebo		Arm 1: 320 Arm 2: 160 Overall: 480 Note: Brain mets. 198 *v* 93 (of total 612 population 198/410 93/202). Of primary analysis set: 148/320 *v* 71/160	Arm 1: 404 Arm 2: 197 Overall: 601	Secondary outcome PFS: in % of those with brain metastases in total population Out of 291, 106/198 events, 7.6 months (95% CI, 6.2 to 9.5) *v* 51/93, 5.4 months (95% CI, 4.1 to 5.7) Risk of disease progressions or death in this subgroup, HR 0.48 (95% CI, 0.34 to 0.69)	OS prespecified Brain mets 114 deaths/291, HR 0.58 (95% CI, 0.40 to 0.85)	
Lin et al[15]	> Second-line	Trastuzumab plus chemotherapy Other: tucatinib	Trastuzumab plus chemotherapy Placebo		Of total 612 population 198/410 93/202		CNS-PFS Arm 1: 9.9 months (95% CI, 8.0 to –13.9) Arm 2: 4.2 months (95% CI, 3.6 to 5.7) Statistic and significance: HR 0.32 (95% CI, 0.22 to 0.48), $P < .00001$ Note: CNS-PFS No. of events per 1,000—intervention: 71/198 No. of events per 1,000—control: 46/93	Arm 1: 18.1 months (95% CI, 15.5 to –) Arm 2: 12.0 months (95% CI, 11.2 to 15.2) Statistic and significance: HR, 0.58 (95% CI, 0.40 to 0.85), $P = .005$ Note: OS in subgroup No. of events per 1,000—intervention: 68/198 No. of events per 1,000—control: 46/93	Arm 1: ORR-IC: 47.3% (95% CI, 33.7 to 61.2) Arm 2: 20.0% (95% CI, 5.7 to 43.7), $P = .03$ Note: ORR-IC investigator in patients with active BMs and measurable intracranial lesions at baseline
Montemurro et al[17] Montemurro et al[14] Note: post hoc exploratory analysis	≥ Second-line	Trastuzumab emtansine (TDM-1) alone	Other		Baseline CNS mets: 398/2,002 overall participants 126 measurable BM at baseline		ORR 21.4% (27/126) 3 CR and 24 PR in those with measurable BMs In 398 with baseline BMs, median PFS 5.5 months, median OS 18.9 months	A 30% reduction in the sum of the largest diameters of target brain lesions was observed in 42.9% (54/126; 95% CI, 34.1 to 52.0) of patients	

(continued on following page)

TABLE 3. Results Evidence Table (continued)

Reference	Tx Line	Arm 1, Intervention(s)	Arm 2, Intervention(s)	Arm 3, Intervention(s)	No. of Patients Analyzed	No. of Patients Analyzed, Safety	CNS Outcomes (1)	CNS Outcomes (2)	CNS Outcomes (3)
Awada et al[13] Subgroup	First-line	Neratinib plus chemotherapy	Trastuzumab plus chemotherapy		Baseline CNS mets Arm 1: 6/242 Arm 2: 12/237 Overall: 18 2.5% *v* 5.1%)		Incidence of symptomatic or progressive CNS events Arm 1: 20 (8.3%) Arm 2: 41 (17.3%) Statistic and significance: relative risk 0.48 (95% CI, 0.29 to 0.79), *P* = .002	Estimated Kaplan-Meier 2-year incidence of CNS recurrences 16.3% *v* 31.2% (HR, 0.45; 95% CI, 0.26 to 0.78; *P* = .004)	
Saura et al[16] Subgroup	> Second-line	Other targeted tx plus chemotherapy: neratinib	Other targeted tx plus chemotherapy: lapatinib		With brain mets Arm 1: 51 (16.6%) Arm 2: 50 (15.9%) Overall: 621		Secondary outcomes included time to CNS disease intervention, cumulative incidence (locally assessed) 22.8% (95% CI, 15.5 to 30.9) *v* 29.2% (95% CI, 22.5 to 36.1), HR 0.78 (95% CI, 0.60 to 1.01), *P* = .043		

Abbreviations: BM, brain metastases; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; ORR, overall response rate; OS, overall survival; PFS, progression-free survival; tx, treatment.

TABLE 4. Effect of Tucatinib, Trastuzumab, and Capecitabine in Patients With HER2-Positive Advanced Breast Cancer and CNS Metastases

Population: Patients with HER2-positive advanced breast cancer (HER2-CLIMB, Murthy et al,[12] Lin et al[15])
Intervention: HER2-targeted therapy (tucatinib, trastuzumab, and capecitabine) (n = 198/410)
Comparator: HER2-targeted therapy (trastuzumab) plus chemotherapy plus placebo (n = 93/202)

Outcome Time Frame	Study Results and Measurements	Absolute Effect Estimates: Systemic Therapy Control	Absolute Effect Estimates: Tucatinib Combination	Certainty of the Evidence (quality of evidence)	Plain Language Summary
CNS—PFS outcomes (Murthy)	HR: 0.48 (95% CI, 0.34 to 0.69) On the basis of data from 291 patients in 1 study Follow-up 14 months	540 per 1,000	311 per 1,000 Difference: 229 fewer per 1,000 (95% CI, 308 fewer to 125 fewer)	Moderate[a]	Tucatinib combination probably increases CNS—PFS outcomes
CNS—intracranial PFS (Lin)	HR: 0.32 (95% CI, 0.22 to 0.48) On the basis of data from 291 patients in 1 study Follow-up 14 months	495 per 1,000	196 per 1,000 Difference: 299 fewer per 1,000 (95% CI, 355 fewer to 215 fewer)	Moderate Because of potentially serious indirectness[a]	Tucatinib combination probably increases CNS—PFS outcomes 9.9 (95% CI, 8.0 to 13.9) *v* 4.2 (95% CI, 3.6 to 5.7) months
CNS—intracranial OS (Lin)	HR: 0.58 (95% CI, 0.4 to 0.85) On the basis of data from 291 patients in 1 study Follow-up 14 months	495 per 1,000	327 per 1,000 Difference: 168 fewer per 1,000 (95% CI, 256 fewer to 54 fewer)	Moderate Because of potentially serious indirectness[a]	Tucatinib combination probably increases CNS—OS outcomes 18.1 (95% CI, 15.5 to NE) *v* 12.0 (95% CI, 11.2 to 15.2) months

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NE, not estimable; OS, overall survival; PFS, progression-free survival.
[a]Risk of bias: serious. Indirectness: serious, because of the exploratory nature of end points/subgroup analysis; imprecision: no serious. Only data from one study; publication bias: no serious. Mostly commercially funded studies.

may discuss palliative options such as systemic therapy *(preferred)* or repeat reduced-dose WBRT *plus memantine* and/or other palliative care options (Type: Formal and informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

Recommendation 6.3 (diffuse recurrence). If a patient has diffuse recurrence after treatment with SRS, clinicians may discuss palliative options such as WB-*M* + *HA* or systemic therapy, and/or *other palliative care options* (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate).

Notes: For patients with prior treatment and poor prognosis, we refer the reader back to the recommendations for those with poor prognosis for those without prior CNS treatment.

Clinical Question 2: Systemic Therapy

How should systemic therapy be managed in patients with HER2-positive brain metastases (including management of systemic therapy when the brain is the only site of progression versus when progression occurs in both the brain and elsewhere)?

Clinical Question 2.1: Upfront Therapy

Patients with asymptomatic brain metastases who have not yet received local therapy.

Recommendation 7.1. The combination of tucatinib, and capecitabine and trastuzumab may be offered to patients with HER2-positive metastatic breast cancer who have brain metastases without symptomatic mass effect and whose disease has progressed on at least one previous

TABLE 5. Effect of T-DM1 in Patients With HER2-Positive Advanced Breast Cancer and CNS Metastases

Population: Patients with HER2-positive advanced breast cancer, prior treatment (Montemurro et al, 2020 and 2019[14,17])
Intervention: T-DM1 (N = 398)
Comparator: None

Outcome Time Frame	Study Results and Measurements	Certainty of the Evidence (quality of evidence)	Plain Language Summary
New brain lesions	On the basis of data from 398 patients in one studies Follow-up 20.6 months	Very low	Median PFS: 5.5 months (95% CI, 5.3 to 5.6) 28.9% (115/398) of patients with baseline BM had new brain lesions. Thirty percent reduction in the sum of the largest diameters of target brain lesions was observed in 42.9% of those with measurable baseline BMs (54/126; 95% CI, 34.1 to 52.0) Median OS: 18.9 months (95% CI, 17.1 to 21.3)

Abbreviations: BM, brain metastases; HER2, human epidermal growth factor receptor 2; OS, overall survival; PFS, progression-free survival; T-DM1, trastuzumab emtansine.

TABLE 6. Effect of Neratinib versus Capecitabine in Patients With HER2-Positive Advanced Breast Cancer and CNS Metastases

Population: patients with HER2-positive advanced breast cancer (Saura, NALA, 2020[16])
Intervention: neratinib plus capecitabine (n = 307)
Comparator: lapatinib plus capecitabine (n = 314)

Outcome Time Frame	Study Results and Measurements	Absolute Effect Estimates		Certainty of the evidence (quality of evidence)	Plain Language Summary
		Lapatinib Plus Capecitabine	Neratinib Plus Capecitabine		
OS	HR: 0.88 (95% CI, 0.72 to 1.07) On the basis of data from 621 patients in one study Follow-up 29.9 months	694 per 1,000	647 per 1,000 Difference: 47 fewer per 1,000 (95% CI, 120 fewer to 24 more)	Moderate open-label[a]	Neratinib plus capecitabine probably has little or no difference on OS
PFS	HR: 0.76 (95% CI, 0.63 to 0.93) On the basis of data from 621 patients in one study Follow-up 29.9 months	710 per 1,000	610 per 1,000 Difference: 100 fewer per 1,000 (95% CI, 168 fewer to 26 fewer)	Moderate open-label[a]	Neratinib plus capecitabine probably slightly increases PFS
STEAEs	Relative risk: 1.14 (95% CI, 0.90 to 1.43) On the basis of data from 614 patients in one study Follow-up 29.9 months	299 per 1,000	341 per 1,000 Difference: 42 more per 1,000 (95% CI, 30 fewer to 129 more)	Moderate open-label[a]	Neratinib plus capecitabine probably has little or no difference on STEAEs
Time to CNS disease intervention	On the basis of data from 621 patients in one study Follow-up 29.9 months			Moderate open-label[a]	Neratinib plus capecitabine probably has little or no difference on time to CNS disease intervention) 22.8% (95% CI, 15.5 to 30.9) *v* 29.2% (95% CI, 22.5 to 36.1), HR 0.78 (95% CI, 0.60 to 1.01), $P = .043$ (via Gray's methods)

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hazard ratio; OS, overall survival; PFS, progression-free survival; STEAE, serious treatment-emergent adverse events.

[a]Risk of bias: no serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias. Imprecision: no serious. Only data from one study.

HER2-directed therapy for metastatic disease. If these agents are used, local therapy may be delayed until there is evidence of intracranial progression (Type: Evidence based; Evidence quality: Low; Strength of recommendation: Weak).

Literature review update and analysis. One randomized trial with a companion publication of an exploratory analysis was identified by the systematic review.[12,15] HER2CLIMB evaluated a regimen of tucatinib, trastuzumab, and capecitabine in patients whose disease progressed on previous trastuzumab-, pertuzumab-, and/or trastuzumab emtansine–based therapy. 291 of 480 of the study participants had asymptomatic brain metastases (BMs). Inclusion criteria were no prior local treatment, BMs were allowed if < 2 cm, or if > 2 cm if immediate local therapy was not required per investigator assessment of factors such as size, location, and symptoms in concert with local therapist. Up to 2 mg of dexamethasone per day (or equivalent) was allowed for control of BM symptoms. The patients meeting these criteria included those who had received local treatment for CNS metastasis or not, and in some cases, with medical monitor approval.

Overall progression-free survival (PFS) for patients in this subgroup was 7.6 (95% CI, 6.2 to 9.5) versus 5.4 (95% CI, 4.1 to 5.7) months. The hazard ratio (HR) was 0.48 (95% CI, 0.34 to 0.69).[12]

The exploratory analysis was of the subgroup of patients with BMs.[15] The outcome was CNS-PFS, defined as the time from random assignment to CNS progression or death from any cause.

CNS-PFS results were (risk of intercranial progression or death) 9.9 (95% CI, 9 to 13.9) versus 4.2 (95% CI, 3.6 to 5.7) months, HR 0.32 (95% CI, 0.22 to 0.48), $P < .00001$. In the exploratory OS and overall response rate outcomes, the results were statistically significant (HR, 0.58; 95% CI, 0.40 to 0.85; $P = .005$).

Clinical interpretation. The principal consideration for the recommendation strength and content is related to the question of an asymptomatic single brain metastasis < 3 cm (> 2 cm metastases were eligible for HER2CLIMB with monitor approval). The new recommendation is limited to patients with asymptomatic brain metastases who have not yet received local therapy, meeting the eligibility criteria regarding failure of prior treatment lines—trastuzumab and pertuzumab or trastuzumab emtansine (T-DM1). However, the Lin et al[15] analysis of HER2CLIMB did not describe the

TABLE 7. Effect of Neratinib Plus Chemotherapy in Patients With HER2-Positive Advanced Breast Cancer and CNS Metastases

Population: Patients with HER2-positive advanced breast cancer (Awada et al[13])
Intervention: HER2-targeted therapy (neratinib plus chemotherapy)
Comparator: Trastuzumab plus chemotherapy

Outcome Time Frame	Study Results and Measurements	Absolute Effect Estimates		Certainty of the evidence (quality of evidence)	Plain Language Summary
		Trastuzumab Plus Chemotherapy	HER2-Targeted Therapy (neratinib plus chemotherapy)		
PFS	HR: 1.02 (95% CI, 0.87 to 1.27) On the basis of data from 479 patients in one study Follow-up 23 (IQR, 13.8-32.3) months	658 per 1,000	665 per 1,000 Difference: 7 more per 1,000 (95% CI, 51 fewer to 86 more)	Moderate Because of potentially serious risk of bias[a]	HER2-targeted therapy (neratinib plus chemotherapy) probably has little or no difference on PFS
ORR	HR: -2.8 (95% CI, –10.5 to 4.8) On the basis of data from 479 patients in studies Follow-up 23 (IQR, 13.8-32.3) months	776 per 1,000	748 per 1,000 Difference: 28 more per 1,000 (95% CI, NE)	Moderate Because of potentially serious risk of bias[a]	HER2-targeted therapy (neratinib plus chemotherapy) probably has little or no difference on objective response rate
TEAEs	Relative risk: 1.26 (95% CI, 1.08 to 1.47) On the basis of data from 474 patients in one study Follow-up 23 (IQR, 13.8-32.3) months	511 per 1,000	644 per 1,000 Difference: 133 more per 1,000 (95% CI, 41 more to 240 more)	Moderate Because of potentially serious risk of bias[a]	HER2-targeted therapy (neratinib plus chemotherapy) probably worsens TEAEs
CNS—incidence	Relative risk: 0.48 95% CI, 0.29 to – 0.79) On the basis of data from 474 patients in one study Follow-up 23 (IQR, 13.8-32.3) months	173 per 1,000	83 per 1,000 Difference: 90 fewer per 1,000 (95% CI, 123 fewer to 36 fewer)	Very low Because of potentially serious risk of bias[a]	We are uncertain whether HER2-targeted therapy (neratinib plus chemotherapy) increases or decreases CNS incidence (on the basis of 61 patients with CNS events)

Abbreviations: HER2, human epidermal growth factor receptor 2; HR, hazard ratio; IQR, interquartile range; NE, not estimable; ORR, overall response rate; PFS, progression-free survival; TEAE, treatment emergent adverse event.

[a]Risk of bias: serious. Lack of blinding of participants and personnel, resulting in potential for performance bias. The accrual goal was reduced from 1,200 to 480 patients, and subsequently the study was no longer powered as a randomized phase III study. Study objective revised. Imprecision: no serious. Only data from one study. Publication bias: no serious. Mostly commercially funded studies.

pretreatment size distribution of treated metastases specifically.

For patients with metastasis < 3-4 cm without symptomatic mass effect with favorable prognosis, discussion of the HER2CLIMB systemic therapy may be reasonable; however, the recommendation strength is weak as the size-specific outcomes were not presented. A discussion to defer local therapy with patients by medical oncology must include input from a MDT that includes a neurosurgeon and a radiation oncologist.

Clinical Question 2.2: Systemic Therapy After Local Therapy

Is there a role for systemic therapy specifically to treat progressive or symptomatic brain metastases in HER2-positive breast cancer?

Recommendation 8.1 (brain recurrence and systemic therapy). For a patient who receives a standard surgical or radiotherapy-based approach to treat brain metastases and is receiving anti-HER2–based therapy and whose systemic disease is not progressive at the time of brain metastasis diagnosis, clinicians should not switch systemic therapy (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Moderate) (no change).

Recommendation 8.2. For a patient who receives a standard surgical and/or radiotherapy-based approach to treatment of brain metastases and whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer[3] (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Moderate) (no change).

Qualifying statement. Recommendation 8.2 applies with one exception. In addition to trastuzumab deruxtecan in the

second-line setting, the HER2CLIMB regimen of tucatinib and capecitabine and trastuzumab may be offered to patients with stable brain metastases after local therapy.

Systemic Treatment for Brain Metastases

Recommendation 9.1. If a patient develops intracranial disease progression after WBRT or SRS (including when a patient is not a candidate for reirradiation), clinicians may discuss offering systemic therapy using a regimen with some evidence of activity in the setting of CNS disease (Type: Formal consensus; Evidence quality: Intermediate; Strength of recommendation: Moderate) (no substantive change).

Note that examples of circumstances in which a patient would not be a candidate for reirradiation include when the patient has already received WBRT plus memantine and there is a desire not to retreat with WBRT plus memantine, when a patient's disease has progressed within a lesion previously treated with SRS, and when a patient's disease has had short or no control with a prior radiotherapy-based approach.

Selected examples of regimens with CNS activity discussed in the 2014 guideline included capecitabine (on the basis of case series and phase I data), lapatinib plus capecitabine (on the basis of several phase II trials), anthracyclines (on the basis of case series), and platinum agents (on the basis of phase II trials).[1] Newer regimens are discussed in the literature review update and analysis section.

There is now one large subset of a randomized phase III trial evaluating systemic approaches in patients with progressive CNS metastases in breast cancer.[15]

Literature Review Update and Analysis

1. Tucatinib, and capecitabine and trastuzumab—Lin et al[15] subgroup analysis of Murthy et al[12] (HER2CLIMB)—see Recommendation 7.1.

2. Neratinib plus capecitabine. Saura et al[16] published a phase III study (NALA) of neratinib plus capecitabine versus lapatinib plus capecitabine for patients who received ≥ second-line systemic therapy, with a subgroup analysis of patients with asymptomatic BMs (111 of 621 of total patients with and without BMs). There was not a statistically significant difference in OS between arms. Secondary outcomes of the study included cumulative incidence of intervention of CNS disease and there was a statistically significant difference (this end point reflects competing risks) favoring neratinib plus chemotherapy.

3. T-DM1. Montemurro et al[14] (KAMILLA) conducted a study of T-DM1 for patients with prior HER2-targeted therapy and chemotherapy and asymptomatic or untreated BM or controlled BM. The publication was of a post hoc exploratory analysis of a cohort of a phase IIIb trial.[14] The investigators showed the results of 398 patients who had received ≥ second-line systemic therapy for HER2-positive metastatic breast cancer with BMs at baseline; 115 of 398 patients experienced disease progression because of new brain metastases. One hundred twenty-six of those participants had measurable brain lesions, in which overall response rate was 21.4%. In 398 participants with baseline BMs, median PFS was 5.5 months and median OS was 18.9 months. Because of the study design (ongoing study, it lacked a comparison arm, and was a post hoc exploratory analysis), the Expert Panel cannot make a recommendation on the basis of these data. If additional prospective, comparative controlled studies on this regimen are published, the Expert Panel will consider in future updates.

4. Neratinib plus paclitaxel. Awada et al[13] (NEfERT-T) published a subgroup analysis of patients who had not received prior treatment in a phase II trial that measured incidence of symptomatic CNS metastases or progressive CNS metastases. The intervention was neratinib plus paclitaxel versus trastuzumab plus paclitaxel. The patients experienced 61 CNS events across both arms (20 with neratinib plus paclitaxel and 41 in trastuzumab plus paclitaxel). The relative risk was 0.48 (95% CI, 0.29 to 0.79), $P = .002$.

However, this was a subgroup analysis and the evidence is insufficient to make a recommendation for this intervention in first-line and requires further study. Without more data, the Panel cannot extrapolate to later lines of therapy.

5. Lapatinib plus capecitabine. The evidence was discussed in the 2014 version of this guideline, and this guideline does not re-review the data.

Clinical Interpretation

- Studies suggest neratinib has CNS activity.
- Although research on neratinib plus chemotherapy is ongoing, the published evidence is insufficient to make a recommendation beyond when patients have received second-line systemic therapy.
- The evidence is insufficient to make a recommendation for a specific drug or regimen over another in this setting (symptomatic brain metastases without local therapy option).
- Clinical trial enrollment should be considered when an appropriate trial is available.

Future Research and Emerging Evidence

- Since the closing date parameters of the systematic literature review, Lin et al[18] published an interim analysis of an ongoing trial of pertuzumab plus high-dose trastuzumab in patients with progressive brain metastases and HER2-positive metastatic breast cancer. The study did not meet inclusion criteria for sample size. This is emerging evidence, and the Expert Panel will discuss future data if available in future updates.
- Neratinib plus chemotherapy research is ongoing.

A study that did not meet inclusion criteria, a phase II trial of neratinib and capecitabine for patients with HER2-positive MBC and brain metastases, was also found. The limitations listed previously apply.[20]

- The Panel is also aware of a San Antonio Breast Cancer 2020 presentation on the neratinib plus capecitabine versus lapatinib plus capecitabine regimen; however, abstracts are excluded as evidence.[10] The evidence is insufficient to make a recommendation in second-line and the Expert Panel will await a full publication and publications on other studies of this regimen.
- In addition to compounds previously discussed, a subgroup of patients receiving trastuzumab deruxtecan who have stable metastases, in the DESTINY 0-1 study, showed sustained response of 18.1 versus 16.4 months, regardless of CNS metastases. Because investigators presented this in an ASCO abstract that is not yet published, additional study is warranted.[21]

Clinical Question 3

Should patients with HER2-positive breast cancer be screened for development of brain metastases?

Recommendation 10.1 (screening). If a patient does not have a known history or symptoms of brain metastases, *there are insufficient data to recommend for or against* performing routine surveillance with brain magnetic resonance imaging (MRI). *Clinicians and patients may discuss options using shared decision-making processes* (Type: Formal and informal consensus; Evidence quality: Low; Strength of recommendation: Weak).

Clinical interpretation. The Expert Panel decided to change this recommendation from recommending against routine surveillance to stating the evidence was insufficient. As evidence is emerging regarding systemic therapy with CNS penetrance and some studies include patients with asymptomatic CNS metastases, the Expert Panel will monitor the literature regarding this. The Expert Panel encourages patients to enroll in clinical trials to expand knowledge regarding MRI surveillance.

Recommendation 10.2. Clinicians should have a low threshold for performing diagnostic brain MRI testing in the setting of any neurologic symptoms suggestive of brain involvement, such as new-onset headaches, unexplained nausea or vomiting, or change in motor or sensory function (Type: Formal consensus; Evidence quality: Low; Strength of recommendation: Strong) (no change).

Note that this recommendation reflects the high prevalence of brain metastases in patients with HER2-positive metastatic breast cancer and longer survival, as described in the Background section. Suggestive symptoms may include new headaches, vertigo, nausea and vomiting, and/or gait disturbance.

PATIENT AND CLINICIAN COMMUNICATION

This section is based on patient and clinician experience and selected literature, but it was not part of the systematic review of the literature. A separate literature search did not find data specific to communication and management of patients with HER2-positive metastatic disease. Although there are differences between issues facing patients with different types of metastatic solid tumors, clinicians are encouraged to refer to a similar discussion in the ASCO 2009 version of the ASCO stage IV non–small-cell lung cancer guideline and to literature on risk communication for patients with cancer.[22,23] A patient who is newly diagnosed with metastatic disease versus one for whom first- and/or second-line or greater treatment has failed will likely face some different issues, although clinical teams are encouraged to discuss the option of clinical trials regardless. Clinicians should consider issues relevant to communicating with patients with metastatic breast cancer, including the importance of evidence-based treatment, and issues for patients and families of those with brain metastases, referring to patients to Cancer.Net links and psychosocial support and introducing concepts of concurrent palliative and antitumor therapies.[24-27]

Research in discussing issues specific to patients with HER2-positive metastatic disease is still needed. Teams should be prepared to present the information in this guideline in a format tailored to the patient's and/or caregiver's learning style. Clinicians are encouraged to conduct discussions with patients that include key subjects of the guideline and reference the sample talking points offered in the 2014 Data Supplement. For recommendations and strategies to optimize patient-clinician communication, see Patient-Clinician Communication: American Society of Clinical Oncology Consensus Guideline.[22]

HEALTH DISPARITIES

Although ASCO clinical practice guidelines represent expert recommendations on the best practices in disease management to provide the highest level of cancer care, it is important to note that many patients have limited access to medical care or receive fragmented care. Factors such as race and ethnicity, age, socioeconomic status, sexual orientation and gender identity, geographic location, and insurance access are known to affect cancer care outcomes.[28] Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Patients with cancer who are members of racial and/or ethnic minorities suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving fragmented care or poor-quality care than other Americans.[29-31]

Many other patients lack access to care because of their age, geography, and distance from appropriate treatment facilities. Awareness of these disparities in access to care should be considered in the context of this clinical practice guideline, and health care providers should strive to deliver the highest[32] level of cancer care to these vulnerable populations. Additionally, stakeholders should work toward achieving health equity by ensuring equitable access to both high-quality cancer care and research and addressing the structural barriers that preserve health inequities.[28]

The systemic guideline[3] includes discussion specific to patients with HER-positive metastatic breast cancer.

MULTIPLE CHRONIC CONDITIONS

Creating evidence-based recommendations to inform treatment of patients with additional chronic conditions, a situation in which the patient may have two or more such conditions—referred to as multiple chronic conditions (MCC)—is challenging. Patients with MCCs are a complex and heterogeneous population, making it difficult to account for all of the possible permutations to develop specific recommendations for care. In addition, the best available evidence for treating index conditions, such as cancer, is often from clinical trials, the study selection criteria of which may exclude these patients to avoid potential interaction effects or confounding of results associated with MCC. As a result, the reliability of outcome data from these studies may be limited, thereby creating constraints for expert groups in making recommendations for care in this heterogeneous patient population.

Because many patients for whom guideline recommendations apply present with MCCs, any management plan needs to take into account the complexity and uncertainty created by the presence of MCCs and highlight the importance of shared decision making around guideline use and implementation. Therefore, in consideration of recommended care for the target index condition, clinicians should review all other chronic conditions present in the patient and take those conditions into account when formulating the treatment and follow-up plans.

Taking these considerations into account, practice guidelines should provide information on how to apply the recommendations for patients with MCC, perhaps as a qualifying statement for recommended care. This may mean that some or all of the recommended care options are modified or not applied, as determined by best practice in consideration of any MCC.[33]

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed for implementation across health settings. Each ASCO guideline includes a member from ASCO's Practice Guideline Implementation Network (PGIN) on the panel. The additional role of this PGIN representative on the guideline panel is to assess the suitability of the recommendations to implementation in the community setting, but also to identify any other barrier to implementation a reader should be aware of. Barriers to implementation include the need to increase awareness of the guideline recommendations among front-line practitioners and survivors of cancer and caregivers, and also to provide adequate services in the face of limited resources. The guideline Bottom Line Box was designed to facilitate implementation of recommendations. This guideline will be distributed widely through the ASCO PGIN. ASCO guidelines are posted on the ASCO website and most often published in the *Journal of Clinical Oncology*.

EXTERNAL REVIEW AND OPEN COMMENT

The draft recommendations were released to the public for open comment from October 15, 2021, through October 29, 2021. Response categories of "Agree as written," "Agree with suggested modifications" and "Disagree. See comments" were captured for every proposed recommendation with 11 written comments received. A total of 99% of the responses either agreed or agreed with slight modifications to the recommendations, whereas 1% of responses disagreed. The Expert Panel members reviewed comments from all sources and determined whether to maintain original draft recommendations, revise with minor language changes, or consider major recommendation revisions. All changes were incorporated before Evidence Based Medicine Committee review and approval.

LIMITATIONS OF THE RESEARCH AND FUTURE DIRECTIONS

Limitations of the research include the lack of specific data on patients with HER2-positive metastatic breast cancer, how to measure efficacy, efficacy of various chemotherapy agents, the benefits and risks of lapatinib alone or with capecitabine, and long-term toxicities of radiation therapy. When there is a lack of multiple robust comparative studies, this precludes strong recommendations on the basis of high-quality evidence. The Expert Panel strongly urges researchers to conduct such trials.

ASCO believes that cancer clinical trials are vital to inform medical decisions and improve cancer care and that all patients should have the opportunity to participate.

ADDITIONAL RESOURCES

More information, including a supplement with additional evidence tables, slide sets, and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines. Patient information is available at www.cancer.net.

RELATED ASCO GUIDELINES

- Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer[3] (https://ascopubs.org/doi/10.1200/jco.22.00519)
- Integration of Palliative Care into Standard Oncology Practice[34] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[22] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- Treatment for Brain Metastases: ASCO-SNO-ASTRO Guideline[5] (https://ascopubs.org/doi/full/10.1200/JCO.21.02314)

AFFILIATIONS

[1]Orlando Health Cancer Institute, Orlando, FL
[2]Duke University, Durham, NC
[3]Dana-Farber Cancer Institute, Boston, MA
[4]University of Michigan, Ann Arbor, MI
[5]American Society of Clinical Oncology, Alexandria, VA
[6]Memorial Sloan Kettering Cancer Center, New York, NY
[7]Seattle Cancer Care Alliance, Seattle, WA
[8]Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA
[9]Institute Gustave Roussy, Villejuif, France
[10]Hematology/Oncology Associates of Central New York, East Syracuse, NY
[11]Texas Oncology, Austin, TX
[12]Patient Advocate, Ann Arbor, MI
[13]University of Texas MD Anderson, Houston, TX

CORRESPONDING AUTHOR

American Society of Clinical Oncology, 2318 Mill Rd, Suite 800, Alexandria, VA 22314; e-mail: guidelines@asco.org.

EDITOR'S NOTE

This American Society of Clinical Oncology (ASCO) Clinical Practice Guideline provides recommendations, with comprehensive review and analyses of the relevant literature for each recommendation. Additional information, including a supplement with additional evidence tables, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

EQUAL CONTRIBUTION

N.R. was the Expert Panel Chair.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at DOI https://doi.org/10.1200/JCO.22.00520.

AUTHOR CONTRIBUTIONS

Conception and design: All authors
Administrative support: Sarah Temin
Collection and assembly of data: All authors
Data analysis and interpretation: All authors
Manuscript writing: All authors
Final approval of manuscript: All authors
Accountable for all aspects of the work: All authors

ACKNOWLEDGMENT

The Expert Panel wishes to thank Dr Michele Halyard, Dr Anthony Provenzano, and the full Evidence Based Medicine Committee for their thoughtful reviews and insightful comments on this guideline.

REFERENCES

1. Ramakrishna N, Temin S, Chandarlapaty S: Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 32:2100-2108, 2014.
2. Sperduto PW, Mesko S, Li J, et al: Beyond an updated graded prognostic assessment (Breast GPA): A prognostic index and trends in treatment and survival in breast cancer brain metastases from 1985 to today. Int J Radiat Oncol Biol Phys 107:334-343, 2020
3. Giordano SH, Franzoi MAB, Temin S: Systemic therapy for advanced human epidermal growth factor receptor 2–positive breast cancer: ASCO guideline update. J Clin Oncol 10.1200/JCO.22.00519
4. Wolff AC, Hammond MEH, Allison KH, et al: Human epidermal growth factor receptor 2 testing in breast cancer: American Society of Clinical Oncology/College of American Pathologists clinical practice guideline focused update. Arch Pathol Lab Med 142:1364-1382, 2018
5. Vogelbaum MA, Brown PD, Messersmith H: Treatment for brain metastases: ASCO/SNO/ASTRO guideline. J Clin Oncol 40:492-516, 2022
6. Cumpston M, Li T, Page MJ, et al: Updated guidance for trusted systematic reviews: A new edition of the Cochrane handbook for systematic reviews of interventions. Cochrane Database Syst Rev 10:Ed000142, 2019
7. Balshem H, Helfand M, Schunemann HJ, et al: GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 64:401-406, 2011
8. Nabors LB, Portnow J, Ahluwalia M, et al: Central nervous system cancers, version 3.2020, NCCN clinical practice guidelines in oncology. J Natl Compr Canc Netw 18:1537-1570, 2020
9. Brown PD, Pugh S, Laack NN, et al: Memantine for the prevention of cognitive dysfunction in patients receiving whole-brain radiotherapy: A randomized, double-blind, placebo-controlled trial. Neuro Oncol 15:1429-1437, 2013
10. Saura C, Ryvo L, Hurvitz S, et al: PD13-09. Impact of neratinib on outcomes in HER2-positive metastatic breast cancer patients with central nervous system disease at baseline: Findings from the phase 3 NALA trial. Presented at the San Antonio Breast Cancer Symposium, San Antonio, TX, 2020
11. Brown PD, Gondi V, Pugh S, et al: Hippocampal avoidance during whole-brain radiotherapy plus memantine for patients with brain metastases: Phase III trial NRG Oncology CC001. J Clin Oncol 38:1019-1029, 2020
12. Murthy RK, Loi S, Okines A, et al: Tucatinib, trastuzumab, and capecitabine for HER2-positive metastatic breast cancer. N Engl J Med 382:597-609, 2020
13. Awada A, Colomer R, Inoue K, et al: Neratinib plus paclitaxel vs trastuzumab plus paclitaxel in previously untreated metastatic ERBB2-positive breast cancer: The NEfERT-T randomized clinical trial. JAMA Oncol 2:1557-1564, 2016
14. Montemurro F, Delaloge S, Barrios CH, et al: Trastuzumab emtansine (T-DM1) in patients with HER2-positive metastatic breast cancer and brain metastases: Exploratory final analysis of cohort 1 from KAMILLA, a single-arm phase IIIb clinical trial☆. Ann Oncol 31:1350-1358, 2020
15. Lin NU, Borges V, Anders C, et al: Intracranial efficacy and survival with tucatinib plus trastuzumab and capecitabine for previously treated HER2-positive breast cancer with brain metastases in the HER2CLIMB trial. J Clin Oncol 38:2610-2619, 2020
16. Saura C, Oliveira M, Feng YH, et al: Neratinib plus capecitabine versus lapatinib plus capecitabine in HER2-positive metastatic breast cancer previously treated with ≥ 2 HER2-directed regimens: Phase III NALA trial. J Clin Oncol 38:3138-3149, 2020
17. Montemurro F, Ellis P, Anton A, et al: Safety of trastuzumab emtansine (T-DM1) in patients with HER2-positive advanced breast cancer: Primary results from the KAMILLA study cohort 1. Eur J Cancer 109:92-102, 2019
18. Lin NU, Pegram M, Sahebjam S, et al: Pertuzumab plus high-dose trastuzumab in patients with progressive brain metastases and HER2-positive metastatic breast cancer: Primary analysis of a phase II study. J Clin Oncol 39:2667-2675, 2021
19. Sohal DPS, Kennedy EB, Cinar P, et al: Metastatic pancreatic cancer: ASCO guideline update. J Clin Oncol 38:3217-3230, 2020
20. Freedman RA, Gelman RS, Anders CK, et al: TBCRC 022: A phase II trial of neratinib and capecitabine for patients with human epidermal growth factor receptor 2–positive breast cancer and brain metastases. J Clin Oncol 37:1081-1089, 2019

21. Jerusalem GHM, Park YH, Yamashita T: Trastuzumab deruxtecan (T-DXd) in patients with HER2+ metastatic breast cancer with brain metastases: A subgroup analysis of the DESTINY-Breast01 trial. J Clin Oncol 39, 2021 (suppl 15; abstr 526)
22. Gilligan T, Coyle N, Frankel RM, et al: Patient-clinician communication: American Society of Clinical Oncology consensus guideline. J Clin Oncol 35:3618-3632, 2017
23. Fagerlin A, Zikmund-Fisher BJ, Ubel PA: Helping patients decide: Ten steps to better risk communication. J Natl Cancer Inst 103:1436-1443, 2011
24. Azzoli CG, Baker S Jr, Temin S, et al: American Society of Clinical Oncology Clinical Practice Guideline update on chemotherapy for stage IV non-small-cell lung cancer. J Clin Oncol 27:6251-6266, 2009
25. Butow PN, Dowsett S, Hagerty R, et al: Communicating prognosis to patients with metastatic disease: What do they really want to know? Support Care Cancer 10:161-168, 2002
26. Hagerty RG, Butow PN, Ellis PA, et al: Cancer patient preferences for communication of prognosis in the metastatic setting. J Clin Oncol 22:1721-1730, 2004
27. Lux MP, Bayer CM, Loehberg CR, et al: Shared decision-making in metastatic breast cancer: Discrepancy between the expected prolongation of life and treatment efficacy between patients and physicians, and influencing factors. Breast Cancer Res Treat 139:429-440, 2013
28. Patel MI, Lopez AM, Blackstock W, et al: Cancer disparities and health equity: A policy statement from the American Society of Clinical Oncology. J Clin Oncol 38:3439-3448, 2020
29. Howlader N, Noone AM, Krapcho M, et al: SEER Cancer Statistics Review, 1975-2013. Bethesda, MD, National Cancer Institute, 2016
30. American Cancer Society: Cancer Facts & Figures for African Americans 2019-2021. Atlanta, GA, American Cancer Society, 2019
31. UCSW Group: United States Cancer Statistics: 1999–2012 Incidence and Mortality Web-Based Report. Atlanta, GA, US Department of Health and Human Services, Centers for Disease Control and Prevention and National Cancer Institute, 2015
32. Mead H, Cartwright-Smith L, Jones K, et al: Racial and Ethnic Disparities in U.S. Health Care: A Chartbook. New York, NY, Commonweath Fund, 2020
33. American Geriatrics Society Expert Panel on the Care of Older Adults with Multimorbidity: Patient-centered care for older adults with multiple chronic conditions: A stepwise approach from the American Geriatrics Society. J Am Geriatr Soc 60:1957-1968, 2012
34. Ferrell BR, Temel JS, Temin S, et al: Integration of palliative care into standard oncology care: American Society of Clinical Oncology clinical practice guideline update. J Clin Oncol 35:96-112, 2017

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Management of Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases: ASCO Guideline Update

The following represents disclosure information provided by authors of this manuscript. All relationships are considered compensated unless otherwise noted. Relationships are self-held unless noted. I = Immediate Family Member, Inst = My Institution. Relationships may not relate to the subject matter of this manuscript. For more information about ASCO's conflict of interest policy, please refer to www.asco.org/rwc or ascopubs.org/jco/authors/author-center.

Open Payments is a public database containing information reported by companies about payments made to US-licensed physicians (Open Payments).

Naren Ramakrishna
Stock and Other Ownership Interests: Cytecare Cancer Center, Bangalore India
Research Funding: Decimal (Inst)

Carey K. Anders
Honoraria: Eisai, Genentech/Roche, Ipsen, Seattle Genetics, Puma Biotechnology, AstraZeneca, Elucida Oncology, Immunomedics, Athenex
Consulting or Advisory Role: Genentech/Roche, Puma Biotechnology, Eisai, Ipsen, Seattle Genetics, AstraZeneca, Elucida Oncology, Immunomedics
Research Funding: Puma Biotechnology (Inst), Lilly (Inst), Merck (Inst), Nektar (Inst), Tesaro (Inst), Seattle Genetics (Inst), G1 Therapeutics (Inst), Pfizer (Inst), Zion (Inst), Novartis Pharmaceuticals UK Ltd (Inst)
Patents, Royalties, Other Intellectual Property: UpToDate.com, Jones and Bartlett
Travel, Accommodations, Expenses: Eisai

Nancy U. Lin
Stock and Other Ownership Interests: Artera Inc
Consulting or Advisory Role: Seattle Genetics, Puma Biotechnology, Daiichi Sankyo, Denali Therapeutics, AstraZeneca, Prelude Therapeutics, Voyager Therapeutics, Affinia Therapeutics, Pfizer, Olema Pharmaceuticals, Aleta Biotherapeutics
Research Funding: Genentech (Inst), Pfizer (Inst), Seattle Genetics (Inst), Merck (Inst), Zion (Inst), Olema Pharmaceuticals (Inst)
Patents, Royalties, Other Intellectual Property: Royalties for chapter in Up-to-Date regarding management of breast cancer brain metastases; Royalties, Jones & Bartlett

Aki Morikawa
Consulting or Advisory Role: Eisai, Lilly, Seattle Genetics
Research Funding: Lilly (Inst), Merrimack (Inst), Novartis (Inst), Genentech/Roche (Inst), Millennium Pharmaceuticals (Inst), Eisai (Inst), Eisai (Inst), Eisai (Inst), Seattle Genetics (Inst), Pfizer (Inst), Tempus (Inst), Molecular Templates (Inst)
Other Relationship: Taiho Pharmaceutical

Sarat Chandarlapaty
Consulting or Advisory Role: Novartis, Lilly, Paige.ai, Sanofi, Inivata, AstraZeneca/MedImmune
Research Funding: Novartis (Inst), Daiichi Sankyo (Inst), Sanofi (Inst), Lilly (Inst), Paige.ai (Inst)
Patents, Royalties, Other Intellectual Property: Patent pending for (1) targeting mutant ER with ER PROTACS and (2) targeting CDK4/6 with CDK4/6 PROTACS (Inst)
Travel, Accommodations, Expenses: BMS
Other Relationship: WebMD, Targeted Oncology, Peerview
Uncompensated Relationships: Totus Medicines

Ian E. Krop
Employment: Freeline Therapeutics, PureTech, AMAG Pharmaceuticals
Leadership: AMAG Pharmaceuticals, Freeline Therapeutics, PureTech
Stock and Other Ownership Interests: AMAG Pharmaceuticals, Freeline Therapeutics, PureTech
Honoraria: Genentech/Roche, AstraZeneca, Celltrion
Consulting or Advisory Role: Genentech/Roche, Seattle Genetics, Daiichi Sankyo, Macrogenics, Novartis, Merck, Bristol Myers Squibb, AstraZeneca
Research Funding: Genentech (Inst), Pfizer (Inst)

Debra A. Patt
Employment: Texas Oncology, McKesson, MedNax
Leadership: McKesson, Mednax, Texas Oncology
Stock and Other Ownership Interests: Mednax
Consulting or Advisory Role: Pfizer, Roche, AstraZeneca, Amgen
Research Funding: Merck (Inst), Eisai (Inst), Seattle Genetics (Inst), Lilly (Inst)
Travel, Accommodations, Expenses: Pfizer, Amgen

Sharon H. Giordano
This author is a member of the *Journal of Clinical Oncology* Editorial Board. Journal policy recused the author from having any role in the peer review of this manuscript.

No other potential conflicts of interest were reported.

APPENDIX

TABLE A1. Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases Expert Panel Membership

Name	Affiliation or Institution	Role or Area of Expertise
Naren Ramakrishna, MD, PhD (Chair of Brain Metastasis Guideline)	Orlando Health Cancer Institute, Orlando, FL	Radiation Oncology
Nancy E. Davidson, MD, cochair (Systemic Therapy)	Fred Hutchinson Cancer Research Center (and University of Washington), Seattle, WA	Medical Oncology
Sharon H. Giordano, MD, MPH, cochair (Systemic Therapy)	University of Texas MD Anderson Cancer Center, Houston, TX	Medical Oncology
Carey Anders, MD	Duke University, Durham, NC	Medical Oncology
Sarat Chandarlapaty, MD, PhD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical Oncology
Jennie Robertson Crews, MD	Seattle Cancer Care Alliance, Seattle, WA	Medical Oncology/Community Oncology (PGIN)
Maria Alice Franzoi, MD	Institute Gustave Roussy, Villejuif, France	Medical Oncology (ASCO Volunteer Corps)
Jeffrey J. Kirshner, MD	Hematology Oncology Associates of Central New York, East Syracuse, NY	Medical Oncology/Community Oncology (PGIN)
Ian E. Krop, MD, PhD	Dana-Farber Cancer Institute, Boston, MA	Medical Oncology
Jennifer Levinson	Ponte Vedra Beach, FL	Patient Advocate
Nancy U. Lin, MD	Dana-Farber Cancer Institute, Boston, MA	Medical Oncology
Aki Morikawa, MD, PhD	University of Michigan, Ann Arbor, MI	Medical Oncology
Debra A. Patt, MD, MPH, MBA	Texas Oncology, PA, Austin, TX	Medical Oncology
Jane Perlmutter, PhD	Ann Arbor, MI	Patient Advocate
Sarah Temin, MSPH	American Society of Clinical Oncology (ASCO), Alexandria, VA	ASCO Practice Guideline Staff (Health Research Methods)

TABLE A2. Summary of Recommendations

Clinical Question	Recommendation	Evidence Rating
—	***Recommendation 1.0.*** Multidisciplinary collaboration to formulate treatment and care plans and disease management for patients with HER2-positive metastatic breast cancer should be the standard of care.	Type: Evidence based, benefits outweigh harms Evidence quality: Intermediate Strength of recommendation: Strong
Overarching clinical question: What is the appropriate course of treatment for patients with HER2-positive advanced breast cancer and brain metastases?		
Clinical question 1: Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer?	***Recommendation 2.1 (single brain metastasis, favorable prognosis).*** If a patient has a favorable prognosis for survival and a single brain metastasis, the patient should be evaluated by an experienced neurosurgeon for discussion of the option of surgical resection, particularly if the metastasis is > 3-4 cm and/or if there is evidence of symptomatic mass effect	Type: Formal and informal consensus Evidence quality: Intermediate Strength of recommendation: Strong
	Recommendation 2.2. If a patient has a favorable prognosis and a single brain metastasis < 3-4 cm without symptomatic mass effect, clinicians may offer either SRS or surgical resection, depending on the location and surgical accessibility of the tumor, need for tissue diagnosis, and other considerations, such as medical risk factors for surgery and patient preference.	Type: Formal consensus Evidence quality: Intermediate Strength of recommendation: Weak
	Recommendation 2.3. If a patient has a favorable prognosis and a single brain metastasis *< 2 cm* without symptomatic mass effect *and who has an option to proceed with HER2-directed therapy with known CNS activity*, then clinicians and patients may discuss options including *SRS* or *deferring local therapy with a MDT*	Type: Informal consensus Evidence quality: Low Strength of recommendation: Moderate
	Recommendation 2.4. For most patients with brain metastases who undergo surgical resection, clinicians should recommend postoperative *radiotherapy (includes SRS, HSRT, and for large or multiple resection beds, possibility of WB-M + HA)* to the resection bed to reduce the risk of local recurrence	Type: Formal and informal consensus Evidence quality: Intermediate Strength of recommendation: Weak
	Recommendation 2.5. If a patient has a favorable prognosis and a single brain metastasis > 3-4 cm, which clinicians *and a MDT* deem unresectable and unsuitable for SRS, clinicians may discuss the options of HSRT or WB-*M + HA. MDTs should consult with patients in this situation*	Type: Formal and informal consensus Evidence quality: Low Strength of recommendation: Weak
	Recommendation 2.6. After treatment, serial imaging every 2-4 months may be used to monitor for local and distant brain failure (also known as local recurrence or new brain disease)	Type: Formal consensus Evidence quality: Low Strength of recommendation: Weak

(continued on following page)

TABLE A2. Summary of Recommendations (continued)

Clinical Question	Recommendation	Evidence Rating
Recommendation 4.2.2 provides a definition of favorable prognosis		
Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer?	***Recommendation 3.0.*** If a patient has a favorable prognosis and presents with multiple, but limited, metastases (defined as two-four lesions), treatment options depend on the size, resectability, and mass effect of the lesions	—
	Recommendation 3.1. In a patient who presents with limited metastases (defined as two-four lesions) suitable for SRS, clinicians may discuss SRS without WB + M/HA	Type: Formal consensus Evidence quality: Intermediate Strength of recommendation: Weak
	Recommendation 3.2. In a patient with *symptomatic* lesions that are unresectable and unsuitable for SRS *or HSRT*, clinicians may recommend WBRT *plus memantine and, if feasible, hippocampal avoidance* and may discuss SRS after WB-*M + HA*	Type: Formal and informal consensus Evidence quality: Low Strength of recommendation: Weak
	Recommendation 3.3. *For patients with limited metastases < 2 cm and not associated with symptomatic mass effect, and who have an option to proceed with HER2-directed therapy with known CNS activity, then clinicians and patients may discuss deferring local therapy with a MDT* Please see discussion of potential upfront systemic therapy in Clinical question 2	Type: Informal consensus Evidence quality: Low Strength of recommendation: Moderate
	Recommendation 3.4. In a patient who has a large (> 3-4 cm) lesion associated with symptomatic mass effect, clinicians may discuss surgical resection of the larger lesion, if the lesion is deemed resectable. The remaining lesions *and resection bed* may be treated with SRS, HSRT with or without WB-*M + HA*. *Clinicians should also provide symptom management*	Type: Formal consensus Evidence quality: Intermediate Strength of recommendation: Weak
Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer?	Diffuse disease or extensive metastases	
	Recommendation 4.1. If a patient has symptomatic brain leptomeningeal metastases, clinicians may recommend WBRT *plus memantine*. The management of leptomeningeal metastases is complex, and recommendations regarding intrathecal therapy and/or systemic therapy for leptomeningeal metastases are outside the scope of this practice guideline	Type: Formal consensus Evidence quality: Low Strength of recommendation: Moderate
	Recommendation 4.2.1. If a patient has a more favorable prognosis and presents with many diffuse and/or extensive brain metastases (≥ five metastases) without leptomeningeal disease, clinicians may recommend *SRS or* WB-*M + HA. For patients with metastases < 2 cm and not associated with symptomatic mass effect, and who have an option to proceed with HER2-directed therapy with known CNS activity, then clinicians and patients may discuss deferring local therapy with a MDT*	Type: Formal and informal consensus Evidence quality: Low Strength of recommendation: Moderate
	Recommendation 4.2.2. Patients with favorable prognoses are those with good performance status and effective systemic therapy options. The criteria may include KPS > 70, controlled extracranial disease, and/or whether good additional systemic therapy options for extracranial disease are available	Type: Formal consensus Evidence quality: Low Strength of recommendation: Weak

(continued on following page)

TABLE A2. Summary of Recommendations (continued)

Clinical Question	Recommendation	Evidence Rating
Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer?	***Recommendation 5.0 (patients with poor prognosis).*** If a patient has brain metastases and a poor prognosis, clinicians should discuss the options of best supportive care and/or palliative care, which may or may not include radiation therapy, on a case-by-case basis	Type: Formal consensus Evidence quality: Low Strength of recommendation: Weak
	Recommendation 5.1. For a patient with symptomatic brain metastases and poor prognosis, WB-*M* + *HA* may be offered if there is a reasonable expectation of symptomatic improvement that outweighs the acute and subacute treatment-related toxicities, including fatigue and decline in neurocognitive function	Type: Formal consensus Evidence quality: Low Strength of recommendation: Weak
Does the approach to local therapy of brain metastases differ in patients with HER2-positive breast cancer?	***Recommendation 6.0 (patients with intracranial metastases, which progress despite initial therapy).*** If a patient has intracranial metastases, which progress despite initial therapy, treatment options will depend on the patient's prior therapies, burden of disease, performance status, and overall prognosis	—
	Recommendation 6.1 (brain recurrence and prior WBRT; limited recurrence). For a patient with a favorable prognosis and limited recurrence after treatment with WBRT, clinicians may discuss SRS, surgery, systemic therapy, and/or additional palliative options For a patient with a favorable prognosis and limited recurrence after treatment with SRS, clinicians may discuss repeat SRS, surgery, *WB-M + HA*, systemic therapy, *and/or additional palliative options*	Type: Formal and informal consensus Evidence quality: Low Strength of recommendation: Moderate
	Recommendation 6.2 (diffuse recurrence). If a patient has diffuse recurrence after treatment with WBRT, clinicians may discuss palliative options such as systemic therapy *(preferred)* or repeat reduced-dose WBRT *plus memantine* and/or other palliative care options	Type: Formal and informal consensus Evidence quality: Low Strength of recommendation: Weak
	Recommendation 6.3 (diffuse recurrence). If a patient has diffuse recurrence after treatment with SRS, clinicians may discuss palliative options such as *WB-M + HA* or systemic therapy, and/or *other palliative care options*	Type: Formal consensus Evidence quality: Low Strength of recommendation: Moderate
Clinical question 2: Systemic therapy How should systemic therapy be managed in patients with HER2-positive brain metastases (including management of systemic therapy when the brain is the only site of progression versus when progression occurs in both the brain and elsewhere)? **Clinical question 2.1: Upfront therapy** Patients with asymptomatic brain metastases who have not yet received local therapy	***Recommendation 7.1.*** *The combination of tucatinib, and capecitabine and trastuzumab may be offered to patients with HER2-positive metastatic breast cancer who have brain metastases without symptomatic mass effect and whose disease has progressed on at least one previous HER2-directed therapy for metastatic disease. If these agents are used, local therapy may be delayed until there is evidence of intracranial progression*	Type: Evidence based Evidence quality: Low Strength of recommendation: Weak

(continued on following page)

TABLE A2. Summary of Recommendations (continued)

Clinical Question	Recommendation	Evidence Rating
Clinical question 2.2: Systemic therapy after local therapy Is there a role for systemic therapy specifically to treat progressive or symptomatic brain metastases in HER2-positive breast cancer?	***Recommendation 8.1 (brain recurrence and systemic therapy)*** For a patient who receives a standard surgical or radiotherapy-based approach to treat brain metastases and is receiving anti-HER2–based therapy and whose systemic disease is not progressive at the time of brain metastasis diagnosis, clinicians should not switch systemic therapy	Type: Formal consensus Evidence quality: Low Strength of recommendation: Moderate
	Recommendation 8.2. For a patient who receives a standard surgical and/or radiotherapy-based approach to treatment of brain metastases and whose systemic disease is progressive at the time of brain metastasis diagnosis, clinicians should offer HER2-targeted therapy according to the algorithms for treatment of HER2-positive metastatic breast cancer ***Qualifying statement.*** Recommendation 8.2 applies with one exception. In addition to trastuzumab deruxtecan in the second-line setting, the HER2CLIMB regimen of tucatinib and capecitabine and trastuzumab may be offered to patients with stable brain metastases after local therapy.	Type: Formal consensus Evidence quality: Intermediate Strength of recommendation: Moderate
Clinical question 2: Systemic therapy How should systemic therapy be managed in patients with HER2-positive brain metastases (including management of systemic therapy when the brain is the only site of progression *v* when progression occurs in both the brain and elsewhere)?	***Recommendation 9.1.*** If a patient develops intracranial disease progression after WBRT or SRS (including when a patient is not a candidate for reirradiation), clinicians may discuss offering systemic therapy using a regimen with some evidence of activity in the setting of CNS disease	Type: Formal consensus Evidence quality: Intermediate Strength of recommendation: Moderate
Clinical question 3 Should patients with HER2-positive breast cancer be screened for development of brain metastases?	***Recommendation 10.1 (screening).*** If a patient does not have a known history or symptoms of brain metastases, *there are insufficient data to recommend for or against* performing routine surveillance with brain MRI. *Clinicians and patients may discuss options using shared decision-making processes*	Type: Formal and informal consensus Evidence quality: Low Strength of recommendation: Weak
	Recommendation 10.2. Clinicians should have a low threshold for performing diagnostic brain MRI testing in the setting of any neurologic symptoms suggestive of brain involvement, such as new-onset headaches, unexplained nausea or vomiting, or change in motor or sensory function	Type: Formal consensus Evidence quality: Low Strength of recommendation: Strong

Abbreviations: HA, hippocampal avoidance; HER2, human epidermal growth factor receptor 2; HSRT, hypofractionated stereotactic radiotherapy; KPS, Karnofsky performance status; MRI, magnetic resonance imaging; SRS, stereotactic radiosurgery; WB-M, WB plus memantine; WBRT, whole-brain radiotherapy.

TABLE A3. Recommendation Rating Definitions

GRADE (used for updated recommendations)

Term	Definitions
Quality of evidence	
High	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	
Strong	In recommendations for an intervention, the desirable effects of an intervention outweigh its undesirable effects In recommendations against an intervention, the undesirable effects of an intervention outweigh its desirable effects All or almost all informed people would make the recommended choice for or against an intervention
Weak	In recommendations for an intervention, the desirable effects probably outweigh the undesirable effects, but appreciable uncertainty exists In recommendations against an intervention, the undesirable effects probably outweigh the desirable effects, but appreciable uncertainty exists Most informed people would choose the recommended course of action, but a substantial number would not

ASCO (used for recommendations from 2014 and 2018)

Term	Definitions
Quality of evidence	
High	High confidence that the available evidence reflects the true magnitude and direction of the net effect (eg, balance of benefits *v* harms) and further research is very unlikely to change either the magnitude or direction of this net effect
Intermediate	Intermediate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect
Low	Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change the magnitude and/or direction of this net effect
Insufficient	Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. Reliance on consensus opinion of experts may be reasonable to provide guidance on the topic until better evidence is available
Strength of recommendation	
Strong	There is high confidence that the recommendation reflects best practice. This is based on: a. strong evidence for a true net effect (eg, benefits exceed harms); b. consistent results, with no or minor exceptions; c. minor or no concerns about study quality; and/or d. the extent of panelists' agreement Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a strong recommendation
Moderate	There is moderate confidence that the recommendation reflects best practice. This is based on: a. good evidence for a true net effect (e.g., benefits exceed harms); b. consistent results with minor and/or few exceptions; c. minor and/or few concerns about study quality; and/or d. the extent of panelists' agreement Other compelling considerations (discussed in the guideline's literature review and analyses) may also warrant a moderate recommendation
Weak	There is some confidence that the recommendation offers the best current guidance for practice. This is based on: a. limited evidence for a true net effect (eg, benefits exceed harms); b. consistent results, but with important exceptions; c. concerns about study quality; and/or d. the extent of panelists' agreement Other considerations (discussed in the guideline's literature review and analyses) may also warrant a weak recommendation