

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

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Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline provides formal expert consensus–based recommendations. Additional information, which may include Data Supplements, slide sets, patient versions, and clinical tools and resources, is available at www.asco.org/guidelines/her2brainmets, and a companion guideline is available at www.asco.org/guidelines/treatHER2pos.

Authors' disclosures of potential conflicts of interest and author contributions are found at the end of this article.

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ABSTRACT

Purpose

To provide formal expert consensus–based 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.

Methods

The American Society of Clinical Oncology (ASCO) convened a panel of medical oncology, radiation oncology, guideline implementation, and advocacy experts and conducted a systematic review of the literature. When that failed to yield sufficiently strong quality evidence, the Expert Panel undertook a formal expert consensus–based process to produce these recommendations. ASCO used a modified Delphi process. The panel members drafted recommendations, and a group of other experts joined them for two rounds of formal ratings of the recommendations.

Results

No studies or existing guidelines met the systematic review criteria; therefore, ASCO conducted a formal expert consensus–based process.

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. 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. Clinicians should not perform routine magnetic resonance imaging (MRI) to screen for brain metastases, but rather should have a low threshold for MRI of the brain because of the high incidence of brain metastases among patients with HER2-positive advanced breast cancer.

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INTRODUCTION

Approximately 15% to 20% of patients with breast cancer have tumors that overexpress the human epidermal growth factor receptor 2 (HER2) protein.^{1,2} Because of 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.³⁻⁵ Although only a small fraction of patients (1% to 3%) presenting with early-stage breast cancer will relapse with the brain as first

site of recurrence, brain metastases are increasingly common in patients with HER2-positive metastatic breast cancer, with up to half of patients experiencing brain metastases over time.⁶⁻¹⁰ Notably, brain metastases seem to occur in a continuous fashion, with continued events even after many years from initial metastatic diagnosis.^{7,8}

Historically, survival of patients diagnosed with brain metastases has been quite poor.¹¹ 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, based on 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 2 years, and this experience has been borne out in other retrospective studies.^{12,13} Therefore, there is an 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

THE BOTTOM LINE

Recommendations on Disease Management for Patients With Advanced HER2-Positive Breast Cancer and Brain Metastases: ASCO Clinical Practice Guideline

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/caregivers

Methods

- An Expert Panel was convened to develop clinical practice guideline recommendations using an expert consensus process. The Expert Panel was supplemented by a Consensus Ratings Panel.

Key Recommendations

- For patients with a favorable prognosis for survival and a single brain metastasis, treatment options include surgery with postoperative radiation, stereotactic radiosurgery (SRS), whole-brain radiotherapy (WBRT; \pm SRS), fractionated stereotactic radiotherapy (FSRT), and SRS (\pm WBRT), depending on metastasis size, resectability, and symptoms. After treatment, serial imaging every 2 to 4 months may be used to monitor for local and distant brain failure.
- 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, WBRT (\pm SRS), SRS (\pm WBRT), and FSRT for metastases $>$ 3 to 4 cm. For metastases $<$ 3 to 4 cm, treatment options include resection with postoperative radiotherapy. In both cases, available options depend on resectability and symptoms.
- For patients with diffuse disease/extensive metastases and a more favorable prognosis and those with symptomatic leptomeningeal metastasis in the brain, WBRT may be offered.
- For patients with poor prognosis, options include WBRT, best supportive care, and/or palliative care.
- For patients with progressive intracranial metastases despite initial radiation therapy, options include SRS, surgery, WBRT, a trial of systemic therapy, or enrollment onto a clinical trial, depending on initial treatment. For patients in this group who also have diffuse recurrence, best supportive care is an additional option.
- For patients whose systemic disease is not progressive at the time of brain metastasis diagnosis, systemic therapy should not be switched.
- 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.
- If a patient does not have a known history or symptoms of brain metastases, routine surveillance with brain magnetic resonance imaging (MRI) should not be performed.
- Clinicians should have a low threshold for performing diagnostic brain MRI testing in the setting of any neurologic symptoms suggestive of brain involvement.

Additional Resources

More information, including a Data Supplement, a Methodology Supplement with information about evidence quality and strength of recommendations, slide sets, and clinical tools and resources, is available at www.asco.org/guidelines/her2brainmets, and a companion guideline is available at www.asco.org/guidelines/treatHER2pos. Patient information is available there and at www.cancer.net.

on HER2 testing, other than noting that quality HER2 testing is required for appropriate identification and management of HER2-positive patients. The American Society of Clinical Oncology (ASCO) clinical practice guideline¹⁴ on systemic therapy for patients with advanced HER2-positive breast cancer accompanies this article, and the ASCO–College of American Pathologists joint clinical practice guideline update on recommendations for HER2 testing in breast cancer was recently published.¹⁵

This guideline covers the management of patients with HER2-positive breast cancer and brain metastases. The consensus 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 and the companion recommendations for systemic therapy.¹⁴

GUIDELINE QUESTIONS

This clinical practice guideline addresses one overarching question and four sub-questions: First, 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? Four, should patients with HER2-positive breast cancer be screened for development of brain metastases?

METHODS

Guideline Development Process

ASCO convened an Expert Panel on the treatment of patients with advanced HER2-positive breast cancer (Appendix Table A1, online only). A brain metastases writing group (subgroup of Expert Panel) met on several occasions and corresponded frequently through e-mail. The Expert Panel members were asked to contribute to the development of the guideline, provide critical review, and finalize the guideline recommendations. The Expert Panel was supplemented by additional experts recruited to rate their agreement with the drafted recommendations as part of the consensus process. The entire membership of experts is referred to as the Consensus Panel (Data Supplement 7 provides a list of members). All members of the Expert Panel reviewed the draft guideline document, which was then disseminated for external review and submitted to *Journal of Clinical Oncology (JCO)* for peer review and publication. All ASCO guidelines are ultimately reviewed and approved by the ASCO Clinical Practice Guideline Committee before publication.

The recommendations were developed by a multidisciplinary group of experts using evidence from observational studies and clinical experience as a guide. A literature search for evidence on brain metastases was conducted, but no publications met the inclusion criteria (Data Supplement). Therefore, the recommendations were developed by a multidisciplinary group of experts and reviewed by radiation oncologists, neurosurgeons, members of the ASCO Breast Cancer Guidelines Advisory Group, and others using a formal consensus process based on the best available evidence and clinical experience.

The guideline recommendations were crafted, in part, using the Guidelines Into Decision Support (GLIDES) methodology and accompanying

BRIDGE-Wiz software (<http://gem.med.yale.edu/BRIDGE-Wiz>). Ratings for the type of recommendation and strength of the evidence are provided with each recommendation (Methodology Supplement).

Detailed information about the methods used to develop this guideline is available in the Methodology Supplement at www.asco.org/guidelines/her2brainmets, including an overview (panel composition, guideline development process, and revision dates) and descriptions of the formal consensus process and of GLIDES/BRIDGE-Wiz.

Guideline Disclaimer

The clinical practice guideline and other guidance published herein are provided by ASCO to assist providers in clinical decision making. The information herein should not be relied on 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 herein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Furthermore, the information is not intended to substitute for the independent professional judgment of the treating provider, because the information does not account for individual variation among patients. Each recommendation reflects high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like *must*, *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 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 the ASCO Conflicts of Interest Management Procedures for Clinical Practice Guidelines (summarized at <http://www.asco.org/rwc>). Members of the panel completed the ASCO disclosure form, which requires disclosure of financial and other interests that are relevant to the subject matter of the guideline, 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 relationships, consulting arrangements, stock ownership, honoraria, research funding, and expert testimony. In accordance with these procedures, the majority of the members of the panel did not disclose any such relationships.

BACKGROUND

On review of the available evidence, the Expert Panel concluded that the majority of the evidence was insufficient to inform evidence-based recommendations for a traditional ASCO clinical practice guideline. Therefore, ASCO used a formal consensus-based process described in the Methodology Supplement. The data cited for this 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. This discussion is

expanded in Data Supplement 1. Brain metastases are common in patients with advanced HER2-positive breast cancer, with up to half of patients (40% to 50%) experiencing brain relapse before death.⁶⁻⁹ As of the production of this guideline, there were no other published guidelines on the treatment of patients with HER2-positive breast cancer and brain metastases. Existing brain metastasis treatment guidelines, such as those developed by the National Comprehensive Cancer Network, are not disease specific.¹⁶ 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) \geq 70, age, controlled extracranial disease, and/or whether good salvage systemic therapy options for extracranial disease are available.¹⁷ Sperduto et al¹⁸ found that the worst survival in patients with breast cancer brain metastases were those with KPS < 50, age > 60 years, and triple-negative histology. In some studies, although HER2-positive status was associated with relatively good survival, 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,¹⁹ 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, the recommendations on patients with HER2-positive breast cancer with brain metastases were formulated by expert consensus. The ASCO Expert Panel on patients with HER2-positive metastatic breast cancer used a modified Delphi method to achieve formal consensus (Methodology Supplement).²⁰ 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 (Methodology Supplement). 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). A particularly important consideration for patients with HER2-positive breast cancer and brain metastases is the role of WBRT in management of limited brain metastatic disease. WBRT has played an important role in the palliative radiotherapy of patients with brain metastases for more than five decades, with an early case series demonstrating an improvement in survival with WBRT versus historical estimates with supportive care alone.²¹ Although WBRT is effective in palliating symptomatic brain metastases, it can be associated

with short- and long-term complications.^{22,23} WBRT is also associated with significant acute fatigue, which may persist for 3 to 6 months after WBRT and is thought to reflect white matter demyelination injury.²⁴ Of particular concern are the neurocognitive sequelae of WBRT. Late effects of WBRT occurring months to years after treatment may include leukoencephalopathy and vascular injury, resulting in increased risk of stroke.²⁵

The addition of WBRT to surgery for a solitary brain metastasis in a randomized trial that compared outcomes with surgery alone showed improved local and distant brain control, but no improvement in survival (only 10% of patients in this study had breast cancer).²⁶ The addition of WBRT to SRS for one to four brain metastases in a randomized study (7% of patients in this study had breast cancer) was associated with improved local control and decreased distant brain failure, but no survival benefit versus SRS alone.²⁷ In another randomized trial of SRS versus WBRT plus SRS for one to three brain metastases (13% of patients in this study had breast cancer), the addition of WBRT was associated with improved local and distant brain control, but also with increased treatment-related fatigue and neurocognitive decline²² versus SRS alone.^{22,27} Although the omission of WBRT for limited (\leq four metastases) brain metastatic disease is associated with an increased risk of distant brain failure, it has not been shown to diminish survival^{27,28} or duration of functional independence.²⁸

Systemic Therapies

There are currently no systemic therapies approved for use in the treatment of patients with breast cancer and brain metastases. Data are primarily available from single-arm prospective trials and, in some cases, from case series and/or retrospective studies. The recent single-arm phase II LANDSCAPE (Lapatinib Ditosylate and Capecitabine in Treating Patients With Stage IV Breast Cancer and Brain Metastases) trial demonstrated significant brain activity for the combination of lapatinib and capecitabine in patients with HER2-positive brain metastases.²⁹ The CNS objective response rate was 65.9% (95% CI, 50.1 to 79.5; defined as \geq 50% volumetric reduction of CNS lesions in the absence of increased steroid dosing). However, this treatment was associated with a 49% grade 3 to 4 toxicity rate, greater than that seen in the short term with radiation therapy approaches such as WBRT or SRS. The majority of first treatment failures (78%) were in the CNS, with a median failure time of 5.5 months. Most patients were treated with radiation therapy, WBRT, or SRS. The overall survival (OS) of 17 months suggests that the delay of radiation therapy was not harmful. 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. If patients have asymptomatic, low-volume brain metastases and have not received radiation therapy, upfront therapy with lapatinib and capecitabine 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 brain after initial therapy, and the impact on OS is unclear. Not surprisingly, disease burden, tumor subtype, and performance status influence

survival after treatment for intracranial progression. In nonrandomized case series, a subset of patients do seem to derive benefit, at least as measured by reductions in tumor burden or symptoms or in terms of favorable survival.³⁰⁻³⁴

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 radionecrosis and supportive care for patients with brain metastases. 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. Although ASCO has not formally endorsed these guidelines, nor is this a complete list, citations are provided for the readers' reference.^{16,35-39}

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 (Methodology Supplement). 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, and medical oncologists.

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

RECOMMENDATIONS

Recommendation strength is weak for all recommendations, unless otherwise stated.

CLINICAL QUESTION

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

Clinical Question A

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

Recommendation I (single brain metastasis, favorable prognosis). If a patient has a favorable prognosis for survival and a single brain metastasis, he or she should be evaluated by an experienced neurosurgeon for discussion of the option of surgical resection, particularly if the metastasis is > 3 to 4 cm and/or if there is evidence of symptomatic mass effect. Evidence quality: intermediate. Recommendation strength: strong.

IA. If a patient has a favorable prognosis and a single brain metastasis < 3 to 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. Evidence quality: intermediate.

If these patients choose to undergo SRS, clinicians may discuss the options of adding WBRT to SRS versus SRS alone. Evidence quality: intermediate.

IB. For most patients with brain metastases who undergo surgical resection, clinicians should recommend postoperative radiotherapy to the resection bed to reduce the risk of local recurrence. Evidence quality: intermediate.

IC. If a patient has a favorable prognosis and a single brain metastasis > 3 to 4 cm, which is deemed unresectable and unsuitable for SRS, clinicians may discuss the options of WBRT or fractionated stereotactic radiotherapy. Evidence quality: low.

ID. After treatment, serial imaging every 2 to 4 months may be used to monitor for local and distant brain failure. Evidence quality: low.

Note that there is more high-level evidence to support WBRT compared with SRS to the resection cavity. However, routine postoperative WBRT does not seem to confer a survival benefit. Recommendation IIIB provides a definition of favorable prognosis.

Recommendation II (limited metastases [two to four metastases] and favorable prognosis). If a patient has a favorable prognosis and presents with multiple, but limited, metastases (two to four), treatment options depend on the size, resectability, and mass effect of the lesions.

IIA. In a patient who presents with limited metastases suitable for SRS, clinicians may discuss SRS with or without WBRT. Evidence quality: intermediate.

IIB. In a patient who has a large (> 3 to 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 may be treated with SRS with or without WBRT. Evidence quality: intermediate.

IIC. In a patient with lesions that are unresectable and unsuitable for SRS, clinicians may recommend WBRT and may discuss SRS after WBRT. Evidence quality: low.

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

Recommendation III (diffuse disease/extensive metastases): IIIA. If a patient has symptomatic leptomeningeal metastases (specifically in the brain), clinicians may recommend WBRT. The management of leptomeningeal metastases is complex, and recommendations regarding intrathecal therapy or systemic therapy for leptomeningeal metastases are outside the scope of this practice guideline. Evidence quality: low. Recommendation strength: moderate.

IIIB. If a patient has a more favorable prognosis and presents with many diffuse/brain metastases (\geq five metastases), clinicians may recommend WBRT. Patients with favorable prognoses are those with good performance status and effective systemic therapy options. The criteria may include KPS ≥ 70 , age, controlled extracranial disease, and/or whether good salvage systemic therapy options for extracranial disease are available. Evidence quality: low.

Recommendation IV (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. Evidence quality: low.

IVA. For a patient with symptomatic brain metastases and poor prognosis, WBRT 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. Evidence quality: low.

Recommendation V (patients with progressive intracranial metastases despite initial therapy). If a patient has progressive intracranial metastases, treatment options will depend on the patient's prior therapies, burden of disease, performance status, and overall prognosis.

VAI (brain recurrence and irradiation; limited recurrence). For a patient with a favorable prognosis and limited recurrence after treatment with WBRT, clinicians may discuss SRS, surgery, a trial of systemic therapy, or enrollment onto a clinical trial. For a patient with a favorable prognosis and limited recurrence after treatment with SRS, clinicians may discuss repeat SRS, surgery, WBRT, a trial of systemic therapy, or enrollment onto a clinical trial. Evidence quality: low. Recommendation strength: moderate.

VAIIa (diffuse recurrence). If a patient has diffuse recurrence after treatment with WBRT, clinicians may discuss palliative options such as repeat reduced dose WBRT, a trial of systemic therapy, enrollment onto a clinical trial, or best supportive care. Evidence quality: low.

VAIIb (diffuse recurrence). If a patient has diffuse recurrence after treatment with SRS, clinicians may discuss palliative options such as WBRT, a trial of systemic therapy, enrollment onto a clinical trial, or best supportive care. Evidence quality: low. Recommendation strength: moderate.

Clinical Question B

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 brain and elsewhere)?

Recommendation VB (brain recurrence and systemic therapy):

VBI. 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. Evidence quality: low. Recommendation strength: moderate.

VBI. 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. (For example, a patient who has been maintained on single-agent trastuzumab and develops isolated progression in the brain should have his or her brain metastases treated and trastuzumab continued.) Evidence quality: intermediate. Recommendation strength: moderate.

Clinical Question C

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

Recommendation VI (systemic treatment for brain metastases):

VIA. If a patient has asymptomatic, low-volume brain metastases and has not received radiation therapy, clinicians may discuss upfront

therapy with lapatinib and capecitabine as an option. Clinicians should discuss the most recent data and inform patients that radiation therapy in this setting is still the primary option. Evidence quality: low.

VIB. If a patient develops intracranial disease progression after WBRT or SRS (including when patient is not a candidate for reirradiation), clinicians may discuss offering systemic therapy as an alternative, using a regimen with some evidence of activity in the setting of CNS disease. Evidence quality: low.

Note that examples of circumstances in which a patient would not be a candidate for reirradiation include when the patient has already received WBRT and there is a desire not to retreat with WBRT, 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. There are no randomized phase III trials evaluating systemic approaches in patients with progressive CNS metastases in breast cancer. Selected examples of regimens with CNS activity include capecitabine (based on case series/phase I data),^{40,41} lapatinib plus capecitabine (based on several phase II trials),^{29,42,43} anthracyclines (based on case series),^{44,45} and platinum agents (based on phase II trials).⁴⁶ Clinical trial enrollment should be considered when an appropriate trial is available.

Clinical Question D

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

Recommendation VII (screening): VIIA. If a patient does not have a known history or symptoms of brain metastases, clinicians should not perform routine surveillance with brain magnetic resonance imaging. Evidence quality: low.

VIIb. 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, such as new-onset headaches, unexplained nausea/vomiting, or change in motor/sensory function. Evidence quality: low. Recommendation strength: strong.

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/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 and is a summary. An expanded version is available in Data Supplement 6. A separate literature search did not find data specific to the management of patients with HER2-positive advanced disease and brain metastases. 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 stage IV non-small-cell lung cancer guideline (2009)⁴⁷ and to literature on risk communication for patients with cancer.⁴⁸ 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.^{47,49-51}

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 styles. Discussions with patients should include the key subjects and sample talking points offered in the Data Supplement.

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. Racial and ethnic disparities in health care contribute significantly to this problem in the United States. Minority racial/ethnic patients with cancer suffer disproportionately from comorbidities, experience more substantial obstacles to receiving care, are more likely to be uninsured, and are at greater risk of receiving care of poor quality than other North Americans.⁵²⁻⁵⁵ 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 level of cancer care to these vulnerable populations. The systemic guideline¹⁴ 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 \geq two such conditions (referred to as multiple chronic conditions [MCCs]) 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 MCCs. 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 treatment and

follow-up plans (common chronic conditions for patients with breast cancer are listed in Data Supplement 5).

Taking these considerations into account, practice guidelines should provide information on how to apply the recommendations for patients with MCCs, 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.⁵⁶

GUIDELINE IMPLEMENTATION

ASCO guidelines are developed to be implemented in a variety of health settings. Barriers to implementation and application of the guideline recommendations include factors such as the need to increase awareness among front-line practitioners and cancer survivors and also the need to provide adequate services in the face of limited resources.

This guideline does not consider cost-effectiveness analyses. The guideline Bottom Line was designed to facilitate implementation of recommendations. This guideline will also be distributed through the ASCO Practice Guideline Implementation Network and other ASCO communications. ASCO guidelines are posted on the ASCO Web site and most often published in *JCO*.

LIMITATIONS OF THE RESEARCH AND FUTURE DIRECTIONS

Limitations of the research include the lack of specific data on patients with HER2-positive disease, how to measure efficacy, efficacy of various chemotherapy agents, the benefits/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 Data Supplement, a Methodology Supplement with information about the expert consensus process, slide sets, and clinical tools and resources, is available at www.asco.org/guidelines/her2brainmets. Patient information is available at www.cancer.net.

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Appendix**Table A1.** Systemic Therapy for Patients With Advanced HER2-Positive Breast Cancer Expert Panel Members

Name	Affiliation	Role/Area of Expertise
Sharon H. Giordano, MD, panel co-chair	University of Texas MD Anderson Cancer Center, Houston, TX	Medical oncology
Eric P. Winer, MD, panel co-chair	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Nancy U. Lin, MD, writing committee co-lead	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Naren Ramakrishna, MD, PhD, writing committee co-lead	University of Florida Health Cancer Center at Orlando Health, Orlando, FL	Radiation oncology
Sarat Chandarlapaty, MD, PhD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
Jennie R. Crews, MD	PeaceHealth St Joseph Cancer Center, Bellingham, WA	Medical oncology, implementation
Nancy E. Davidson, MD	University of Pittsburgh Cancer Institute and UPMC Cancer Center, Pittsburgh, PA	Medical oncology
Francisco J. Esteva, MD	New York University Cancer Institute, New York, NY	Medical oncology
Ana M. Gonzalez-Angulo, MD, MSc	University of Texas MD Anderson Cancer Center, Houston, TX	Medical oncology
Jeffrey J. Kirshner, MD	Hematology/Oncology Associates of Central New York, East Syracuse, NY	Medical oncology, implementation
Ian Krop, MD, PhD	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Jennifer Levinson	Ponte Vedra Beach, FL	Advocacy
Shanu Modi, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
Debra A. Patt, MD, MPH	Texas Oncology, Austin, TX	Medical oncology, community
Edith A. Perez, MD	Mayo Clinic, Jacksonville, FL	Medical oncology
Jane Perlmutter, PhD	Ann Arbor, MI	Biostatistics, advocacy

NOTE. American Society for Clinical Oncology staff: Sarah Temin.
Abbreviations: HER2, human epidermal growth factor receptor 2; UPMC, University of Pittsburgh Medical Center.