VOLUME 32 · NUMBER 19 · JULY 1 2014

JOURNAL OF CLINICAL ONCOLOGY

ASCO SPECIAL ARTICLE

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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A B S T R A C T

Purpose
To provide evidence-based recommendations to practicing oncologists and others on systemic therapy for patients with human epidermal growth factor receptor 2 (HER2) –positive advanced breast cancer.

Methods
The American Society of Clinical Oncology convened a panel of medical oncology, radiation oncology, guideline implementation, and advocacy experts and conducted a systematic literature review from January 2009 to October 2012. Outcomes of interest included overall survival, progression-free survival (PFS), and adverse events.

Results
A total of 16 trials met the systematic review criteria. The CLEOPATRA trial found survival and PFS benefits for docetaxel, trastuzumab, and pertuzumab in first-line treatment, and the EMILIA trial found survival and PFS benefits for trastuzumab emtansine (T-DM1) in second-line treatment. T-DM1 also showed a third-line PFS benefit. One trial reported on duration of HER2-targeted therapy, and three others reported on endocrine therapy for patients with HER-positive advanced breast cancer.

Recommendations
HER2-targeted therapy is recommended for patients with HER2-positive advanced breast cancer, except for those with clinical congestive heart failure or significantly compromised left ventricular ejection fraction, who should be evaluated on a case-by-case basis. Trastuzumab, pertuzumab, and taxane for first-line treatment and T-DM1 for second-line treatment are recommended. In the third-line setting, clinicians should offer other HER2-targeted therapy combinations or T-DM1 (if not previously administered) and may offer pertuzumab, if the patient has not previously received it. Optimal duration of chemotherapy is at least 4 to 6 months or until maximum response, depending on toxicity and in the absence of progression. HER2-targeted therapy can continue until time of progression or unacceptable toxicities. For patients with HER2-positive and estrogen receptor–positive/progesterone receptor–positive breast cancer, clinicians may recommend either standard first-line therapy or, for selected patients, endocrine therapy plus HER2-targeted therapy or endocrine therapy alone.

J Clin Oncol 32:2078-2099. © 2014 by American Society of Clinical Oncology

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Published online ahead of print at www.jco.org on May 5, 2014.

Clinical Practice Guideline Committee approval: November 19, 2013.

Editor's note: This American Society of Clinical Oncology Clinical Practice Guideline provides recommendations, with review and analyses of the relevant literature for each recommendation. Additional information, including a Data Supplement with additional evidence tables, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information, is available at www.asco.org/guidelines/treatHER2pos, and a companion guideline is available at www.asco.org/guidelines/her2brainmets.

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

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0732-183X/14/3219w-2078w/$20.00

DOI: 10.1200/JCO.2013.54.0948

INTRODUCTION

Over the past decade, many new systemic therapies have become available for the treatment of advanced breast cancer. In particular, the treatment of human epidermal growth factor receptor 2 (HER2)–positive breast cancer has evolved because of the development of HER2-targeted therapies that have been shown to improve survival for patients with early-stage or metastatic breast cancer. Approximately 15% of patients with breast cancer have tumors that overexpress the HER2 protein, and these patients can benefit from HER2-targeted therapies.[1,2] Brain metastases are common in patients with HER2-positive metastatic breast cancer, with up to half of patients experiencing

THE BOTTOM LINE

GUIDELINE QUESTION

What is the optimal medical therapy for advanced human epidermal growth factor receptor 2 (HER2) –positive breast cancer, specifically HER2-targeted therapy, either alone or in combination with chemotherapy and/or endocrine therapy?

Target Population

- Individuals with advanced HER2-positive breast cancer

Target Audience

- Medical oncologists, radiation oncologists, surgeons, oncology nurses, and patients/caregivers

Recommendations

- Clinicians should recommend HER2-targeted therapy–based combinations for first-line treatment, except for highly selected patients with estrogen receptor (ER) –positive or progesterone receptor (PgR) –positive and HER2-positive disease, for whom clinicians may use endocrine therapy alone. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.
- If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy, clinicians should recommend second-line HER2-targeted therapy–based treatment. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.
- If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, clinicians should recommend third-line or greater HER2-targeted therapy–based treatment. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.
- Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.
- If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy, clinicians should recommend trastuzumab emtansine (T-DM1) as second-line treatment. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.
- If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted therapy, but she has not received T-DM1, clinicians should offer T-DM1. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.
- If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, but she has not received pertuzumab, clinicians may offer pertuzumab. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.
- If a patient's HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment, and she has already received pertuzumab and T-DM1, clinicians should recommend third-line or greater HER2-targeted therapy–based treatment. Options include lapatinib plus capecitabine, as well as other combinations of chemotherapy, and trastuzumab, lapatinib and trastuzumab, or hormonal therapy (in patients with ER-positive and/or PgR-positive disease). There is insufficient evidence to recommend one regimen over another. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.
- If a patient is receiving HER2-targeted therapy and chemotherapy combinations, the chemotherapy should continue for approximately 4 to 6 months (or longer) and/or to the time of maximal response, depending on toxicity and in the absence of progression. When chemotherapy is stopped, clinicians should continue the HER2-targeted therapy; no further change in the regimen is needed until the time of progression or unacceptable toxicities. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.
- If a patient finished trastuzumab-based adjuvant treatment $\leq$ 12 months before recurrence, clinicians should follow the second-line HER2-targeted therapy–based treatment recommendations. Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.
- If a patient finished trastuzumab-based adjuvant treatment $>$ 12 months before recurrence, clinicians should follow the first-line HER2-targeted therapy–based treatment recommendations. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.
- If a patient's cancer is hormone receptor positive and HER2 positive, clinicians may recommend either:
  - HER2-targeted therapy plus chemotherapy. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

(continued on following page)

THE BOTTOM LINE (CONTINUED)

- Endocrine therapy plus trastuzumab or lapatinib (in selected cases). Type: evidence based. Evidence quality: high. Strength of recommendation: moderate.
- Endocrine therapy alone (in selected cases). Type: evidence based. Evidence quality: intermediate. Strength of recommendation: weak.

- If a patient has started with an HER2-positive targeted therapy and chemotherapy combination, clinicians may add endocrine therapy to the HER2-targeted therapy when chemotherapy ends and/or when the cancer progresses. Type: informal consensus. Evidence quality: insufficient. Strength of recommendation: weak.
- In special circumstances, such as low disease burden, presence of comorbidities (contradictions to HER2-targeted therapy such as congestive heart failure), and/or presence of a long disease-free interval, clinicians may offer first-line endocrine therapy alone. Type: informal consensus. Evidence quality: intermediate. Strength of recommendation: weak.
- Qualifying statement: Although clinicians may discuss using endocrine therapy with or without HER2-targeted therapy, the majority of patients will still receive chemotherapy plus HER2-targeted therapy.
- Note: The guide for rating recommendations and evidence quality is provided in the Methodology Supplement.

Additional Resources

Additional information, including a Data Supplement, a Methodology Supplement, evidence tables, and clinical tools and resources, can be found at www.asco.org/guidelines/treatHER2pos. Patient information is available there and at www.cancer.net.

brain metastases. Recommendations for the management of brain metastases in patients with HER2-positive breast cancer are detailed in a companion guideline.[3]

The rationale for this guideline is that several new agents have been approved by the US Food and Drug Administration (FDA) for the treatment of metastatic HER2-positive breast cancer since the approval of trastuzumab. This guideline reviews the evidence and provides guidance for optimal management of patients with HER2-positive metastatic breast cancer. A limited portion of the evidence base of this guideline (specifically regarding evidence on trastuzumab published before 2009) was included from two systematic reviews from Cancer Care Ontario (CCO) and from the systematic review by the American Society of Clinical Oncology (ASCO). The ASCO review both updated the CCO search on trastuzumab and included a broader search on additional ASCO clinical questions. The Expert Panel used results from the CCO systematic reviews in formulating recommendations discussed in Questions 1.A.I and 1.B.IV.[4,5] The ASCO recommendations were developed by ASCO and are not based on the CCO recommendations.

This guideline includes recommendations concerning the use of trastuzumab and newer agents in first- and second-line treatment, including combination therapies. Approximately half of all HER2-positive breast cancers are also hormone receptor positive. The dependency of HER2-positive, hormone receptor–positive tumors on estrogen signaling is only partially understood. This guideline addresses what is known about the use of endocrine therapy for patients who have tumors that are both HER2 positive and hormone receptor positive. This guideline will not discuss HER2 testing, other than noting that quality HER2 testing is required for appropriate identification and management of HER2-positive patients. ASCO–College of American Pathologists recommendations for HER2 testing in breast cancer were recently published.[6]

GUIDELINE QUESTIONS

This clinical practice guideline addresses four overarching clinical questions: First, what are the optimal treatments for patients with HER2-positive advanced breast cancer in first-, second-, and third-line treatment and beyond? Second, what are the optimal timing, dose, schedule, and duration of treatment? Third, how should any previous HER2 adjuvant therapy influence treatment? And fourth, how does estrogen receptor (ER)/progesterone receptor (PgR) status influence decisions about treatment of patients with HER2-positive, hormone receptor–positive advanced breast cancer?

METHODS

Guideline Development Process

The recommendations were developed by a multidisciplinary group of experts (Appendix Table A1, online only) using a systematic review of phase III randomized controlled trials (RCTs) and clinical experience as a guide. An ASCO systematic review in Medline was conducted. Most of the recommendations are evidence based and rely on publications found in literature searches from 2009 to October 2012 (trastuzumab) and from 1966 to 2012 (nontrastuzumab agents). Literature on trastuzumab, specifically articles published before 2009, was included in an earlier CCO systematic review (Methodology Supplement). In some selected cases, where evidence was lacking, but there was a high level of agreement among panel members, informal consensus was used (as noted in Bottom Line box).

Articles were selected for inclusion in the systematic review of evidence if they met the following criteria: fully published or recent meeting presentations of English-language reports of phase III RCTs or rigorously conducted systematic reviews or meta-analyses; studies involving a population of patients with HER2-positive advanced breast cancer; and trials comparing a targeted agent (± chemotherapy and ± endocrine therapy) with another treatment regimen, placebo, or observation. Meeting abstracts were included only if the presentation or poster was available.

Articles were excluded from the systematic review if they were: meeting abstracts not subsequently published in peer-reviewed journals; editorials, commentaries, letters, news articles, case reports, or narrative reviews; and published in a language other than English. 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 type of recommendation and strength of evidence are provided in the Methodology and Data Supplements.

Detailed information about the methods used to develop this guideline, regarding the Expert Panel composition, guideline development process, and steps taken in the systematic review and recommendation development process, is available in the Methodology and Data Supplements at www.asco.org/guidelines/treatHER2pos.

Guideline Disclaimer

The clinical practice guidelines 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, 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 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.

Search Results

A total of nine first-line, three second-line, and four beyond–second-line phase III randomized clinical trials were deemed eligible for inclusion in the ASCO systematic review of the results (some trials provided evidence for > one recommendation) and comprise the evidentiary basis of the guideline recommendations, in addition to the trials in the CCO systematic review. The identified trials spanned from 2009 to 2012. The Data Supplement provides additional details of the results of the systematic review.

To address the question of the role of hormonal/endocrine therapy, the systematic review identified three hormonal therapy plus HER2-targeted therapy studies, all in the first-line setting.[7-9] Two studies addressed questions of how prior adjuvant HER2-targeted therapy may influence subsequent treatment choices.[10,11] There was insufficient evidence to make evidence-based recommendations on some of these questions. Therefore, some recommendations were made on the basis of informal consensus and are labeled as such.

Study Quality

As seen in the quality assessment table (Table 1), study quality was formally assessed for the 11 studies identified. Design aspects related to individual study quality were assessed by one reviewer, with factors such as blinding, allocation concealment, placebo control, intention to treat, funding sources, and so on generally indicating an intermediate to high potential risk of bias for most of the identified evidence. The Methodology Supplement provides definitions of ratings for overall potential risk of bias.

RESULTS

More extensive discussion and analysis of the literature review are provided in Data Supplement 6.

CLINICAL QUESTION 1

What is the optimal treatment for patients with HER2-positive advanced breast cancer?

For patients with HER2-positive advanced breast cancer:

Clinical Question 1.A

Is HER2-targeted therapy recommended for all patients in the first-line setting?

Recommendation 1.A.I. Clinicians should recommend HER2-targeted therapy–based combinations for first-line treatment, except for highly selected patients with ER-positive or PgR-positive and HER2-positive disease, for whom clinicians may use endocrine therapy alone (see Clinical Question 2). Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

Literature review and analysis. This recommendation is based on a body of evidence regarding first-line therapy, found both in the ASCO and CCO systematic reviews.[4] CCO included the pivotal trial by Slamon et al[21] and nine other RCTs of trastuzumab. These trials found a benefit for HER2-targeted therapy combinations, specifically with trastuzumab. The study by Slamon et al was the only first-line phase III trial that compared an HER2-targeted therapy plus chemotherapy with chemotherapy alone. That trial found survival, time to progression (TTP), and overall response rate benefits in the trastuzumab arm (see CCO evidence table at https://www.cancercare.on.ca/common/pages/UserFile.aspx?fileId=13,890). The CCO review found two phase III trials that compared HER2-targeted therapy plus endocrine therapy with endocrine therapy alone.[7,8] Both of those trials found progression-free survival (PFS) and TTP benefits, but no overall survival (OS) benefit, in the combination arm and will be discussed in the section on endocrine therapy (Clinical Question 2), along with another more recent trial.[9] A separate ASCO guideline addresses the definition of and testing for HER2 positivity in patients with breast cancer and its role in treatment selection for these patients.[6]

The ASCO systematic review results included five other first-line studies of various trastuzumab plus chemotherapy combinations.[7,8,13-15] The ASCO systematic review also included studies in which patients in the interventional arms received lapatinib, pertuzumab, and/or trastuzumab emtansine (T-DM1).[9-12,16] Selected results of these trials are listed in Tables 2, 3, and 4; results from the trials on recommended agents are discussed here and in the Data Supplement.

Table 1. Quality Assessment

Study	Adequate Randomization	Concealed Allocation	Sufficient Sample Size	Comparable Groups	Blinded	Validated and Reliable Measures	Adequate Follow-Up	ITT	Insignificant COIs	Overall Risk of Bias
Baselga et al[10] (CLEOPATRA; 2012)	+	+	+	?	Partially	+	—	+	—	Intermediate
Blackwell et al,[11] Verma et al[12] (EMILIA; 2012)	+	?	+	+	—	+	+	+	—	Intermediate
Huober et al[7] (eLEcTRA; 2012)	?	?	—	Partially	?	+	?	?[a]	—	High
Kaufman et al[8] (TAnDEM; 2009)	+	?	+	+	—	+	Partially	+[b]	—	High
Schwartzberg et al[9] (2010)	?	?	+	Partially	+	+	?	+[c]	—	High
Andersson et al[13] (HERNATA; 2011)	+	+	+	+	?	+	Partially	+[d]	—	Intermediate
Valero et al[14] (BCIRG 007; 2011)	+	+	+	+	—	+	+	+[e]	—	Intermediate
Inoue et al[15] (JO17360; 2010)	+	+	Partially[f]	+	—	+	?	—[g]	—	Intermediate
Gelmon et al[16] (MA.31/ GSK EGF108919; 2012)	?	?	?	+	?	Partially	Partially	+	—	?
Cameron et al,[17] Geyer et al[18] (EGF100151; 2010)	+	+	—[h]	+	Partially	Partially	?	+	—	High
Blackwell et al[19,20] (EGF104900; 2010, 2012)	?	?	?	+	—	+	+	+[i]	—	High

NOTE. + indicates criterion was met; — indicates criterion was not met; ? indicates insufficient detail, not reported, and/or uncertain risk of bias.
Abbreviations: COI, conflict of interest; HER2, human epidermal growth factor receptor 2; ITT, intent to treat; OS, overall survival.
[a]If patient withdrew from study or was lost to follow-up without recorded tumor progression, their observation was censored at date of last adequate tumor assessment.
[b]For all patients who received ≥ one dose of assigned study drug.
[c]Overall population included patients with HER2-negative disease.
[d]For efficacy. Safety analysis included all participants who received ≥ one dose.
[e]Time to progression, response rate, response duration, and OS.
[f]Met target accrual, but this was < 100 per arm.
[g]For safety. Modified ITT analysis included those patients in safety group, excluding one who did not meet eligibility.
[h]Did not meet target for OS.
[i]For efficacy analysis. Safety analysis included randomly assigned patients who received ≥ one dose.

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