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ASCO SPECIAL ARTICLE

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Clinical Practice Guideline Update

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Clinical Practice Guideline Committee approval: April 4, 2018.

Editor's note: This American Society of Clinical Oncology (ASCO) 2018 Clinical Practice Guideline update reaffirms and summarizes the recommendations that were previously published in 2014; the 2014 recommendations remain current as of April 2018. Additional information, including an abbreviated Data Supplement with new studies, a Methodology Supplement, slide sets, clinical tools and resources, and links to patient information at www.cancer.net, is available at www.asco.org/breast-cancer-guidelines.

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ABSTRACT

Purpose

To update evidence-based guideline recommendations for practicing oncologists and others on systemic therapy for patients with human epidermal growth factor receptor 2 (HER2)–positive advanced breast cancer to 2018.

Methods

An Expert Panel conducted a targeted systematic literature review (for both systemic treatment and CNS metastases) and identified 622 articles. Outcomes of interest included overall survival, progression-free survival, and adverse events.

Results

Of the 622 publications identified and reviewed, no additional evidence was identified that would warrant a change to the 2014 recommendations.

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 trastuzumab emtansine for second-line treatment are recommended. In the third-line setting, clinicians should offer other HER2-targeted therapy combinations or trastuzumab emtansine (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. Additional information is available at www.asco.org/breast-cancer-guidelines.

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INTRODUCTION

The goal of this update is to provide oncologists, other health care practitioners, patients, and caregivers with recommendations regarding guidance for optimal management of patients with HER2-positive metastatic breast cancer.

ASCO first published two evidence-based clinical practice guidelines on optimal management of patients with human epidermal growth factor receptor 2 (HER2)–positive metastatic breast cancer in 2014.[1,2] The goal of this 2018 guideline update is to provide oncologists and other clinicians with current recommendations regarding the treatment of patients with HER2-positive metastatic breast cancer. The current 2018 update assesses whether the 2014 recommendations remain valid. A complete list of previous recommendations is available at www.asco.org/breast-cancer-guidelines and in Data Supplement 1.

METHODS

Guideline Update Process

ASCO uses a "signals"[3] approach to facilitate guideline updating. This approach is intended to identify new,

ASSOCIATED CONTENT

Appendix
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Data Supplement
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THE BOTTOM LINE

Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer: ASCO Clinical Practice Guideline Update

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

Methods

A systematic review of the literature was performed and relevant evidence was evaluated for inclusion into this updated clinical practice guideline using the signals approach.

Recommendations

- Clinicians should recommend HER2-targeted therapy–based combinations for first-line treatment, except for highly selected patients with estrogen receptor–positive or progesterone receptor–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 estrogen

(continued on following page)

THE BOTTOM LINE (CONTINUED)

receptor–positive and/or progesterone receptor–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).
  - 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

More information, including a Data Supplement with additional evidence tables, 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/breast-cancer-guidelines. 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.

potentially practice-changing data—signals—that might translate into revised practice recommendations. The approach relies on routine literature searching and the expertise of ASCO Guideline Panel members to identify signals. The Methodology Supplement available at www.asco.org/breast-cancer-guidelines provides additional information about the signals approach.

PubMed and the Cochrane Library were searched for randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines for the period from October 4, 2011, to overlap with the search for the previous guideline, through August 11, 2017. The disease and intervention search terms were those that were used for the 2014 guideline. An Expert Panel (members listed in Appendix Table A1, online only), formed in accordance with the ASCO Conflict of Interest Management Procedures for Clinical Practice Guidelines, reviewed the abstracts that were identified for predefined signals that would suggest the need to change a previous recommendation. Additional information about the results of the updated literature search (Data Supplement 2) and 2017

search strategy string and results (Data Supplement 3), as well as a discussion of the ASCO signals approach to guideline updating, are available at www.asco.org/breast-cancer-guidelines and in the 2018 Data Supplement and 2018 Methodology Supplement, respectively. A Quality of Reporting of Meta-Analyses diagram of the updated search and the clinical questions are provided in Data Supplements 4 and 5, respectively.

The Expert Panel communicated via telephone and e-mail to consider the evidence for each of the 2018 recommendations. This systematic review–based guideline product was developed by a multidisciplinary Expert Panel, which included patient representatives and an ASCO guidelines staff member with health research methodology expertise. The guideline was circulated in draft form to the Expert Panel. ASCO's Clinical Practice Guidelines Committee leadership reviewed and approved the final document. All funding for the administration of the project was provided by ASCO.

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This is the most recent information as of the publication date. For the most recent information, and to submit new evidence, please visit www.asco.org/breast-cancer-guidelines.

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 http://www.asco.org/rwc). 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.

RESULTS

A joint search for both guidelines yielded 622 publications. After careful review of the identified publications, the Expert Panel concluded that there were no results that would change the 2014 guideline recommendations.[1] A bibliography of the results of the updated literature search is provided in Data Supplement 2.

RECOMMENDATIONS

The 2018 recommendations are listed in the Bottom Line Box. These recommendations are consistent with the previous (2014) recommendations.

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 Data and Methodology Supplements, 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

- Recommendations on Disease Management for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer and Brain Metastases[4] (http://ascopubs.org/doi/10.1200/JCO.2018.79.2713)
- Integration of Palliative Care into Standard Oncology Practice[5] (http://ascopubs.org/doi/10.1200/JCO.2016.70.1474)
- Patient-Clinician Communication[6] (http://ascopubs.org/doi/10.1200/JCO.2017.75.2311)
- American Cancer Society/American Society of Clinical Oncology Breast Cancer Survivorship Care[7] (http://ascopubs.org/doi/10.1200/JCO.2015.64.3809)

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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REFERENCES

1. Giordano SH, Temin S, Kirshner JJ, et al: Systemic therapy for patients with advanced human epidermal growth factor receptor 2-positive breast cancer: American Society of Clinical Oncology clinical practice guideline. J Clin Oncol 32:2078-2099, 2014
2. Ramakrishna N, Temin S, Chandarlapaty S, et al: 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
3. Shojania KG, Sampson M, Ansari MT, et al: How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 147:224-233, 2007
4. Ramakrishna N, Temin S, Chandarlapaty S, et al: Recommendations on disease management for patients with advanced human epidermal growth factor receptor 2–positive breast cancer and brain metastases: ASCO clinical practice guideline update. J Clin Oncol doi:10.1200/JCO.2018.79.2713
5. 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
6. 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
7. Runowicz CD, Leach CR, Henry NL, et al: American Cancer Society/American Society of Clinical Oncology breast cancer survivorship care guideline. J Clin Oncol 34:611-635, 2016

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Appendix

Table A1. Systemic Therapy for Patients With Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer Expert Panel Membership

Name (and Designation)	Affiliation/Institution	Role/Area of Expertise
Nancy E. Davidson, MD, co-chair	Fred Hutchinson Cancer Research Center and University of Washington, Seattle, WA	Medical oncology
Sharon H. Giordano, MD, co-chair	The University of Texas MD Anderson Cancer Center, Houston, TX	Medical oncology
Sarat Chandarlapaty, MD, PhD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
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Jeffrey J. Kirshner, MD	Hematology Oncology Associates of Central New York, East Syracuse, NY	Medical oncology
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Nancy U. Lin, MD	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Shanu Modi, MD	Memorial Sloan Kettering Cancer Center, New York, NY	Medical oncology
Debra A. Patt, MD, MPH, MBA	Texas Oncology, Austin, TX	Medical oncology
Jane Perlmutter, PhD	Ann Arbor, MI	Patient representative
Naren Ramakrishna, MD, PhD	Orlando Health University of Florida Cancer Center, Orlando, FL	Radiation oncology
Eric P. Winer, MD	Dana-Farber Cancer Institute, Boston, MA	Medical oncology
Sarah Temin, MSPH	ASCO	Staff/health research methodologist

Abbreviation: PGIN, Practice Guidelines Implementation Network.