

# 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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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](http://www.asco.org/guidelines/treatHER2pos), and a companion guideline is available at [www.asco.org/guidelines/her2brainmets](http://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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## 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.

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## 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.<sup>1,2</sup> 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.

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## 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](http://www.asco.org/guidelines/treatHER2pos). Patient information is available there and at [www.cancer.net](http://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.<sup>3</sup>

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.<sup>4,5</sup> 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.<sup>6</sup>

## 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 ( $\pm$  chemotherapy and  $\pm$  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](http://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*, *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.<sup>7-9</sup> Two studies addressed questions of how prior adjuvant HER2-targeted therapy may influence subsequent treat-

ment choices.<sup>10,11</sup> 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.<sup>4</sup> CCO included the pivotal trial by Slamon et al<sup>21</sup> 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.<sup>7,8</sup> 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.<sup>9</sup> 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.<sup>6</sup>

The ASCO systematic review results included five other first-line studies of various trastuzumab plus chemotherapy combinations.<sup>7,8,13-15</sup> The ASCO systematic review also included studies in which patients in the interventional arms received lapatinib, pertuzumab, and/or trastuzumab emtansine (T-DM1).<sup>9-12,16</sup> 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 <sup>10</sup> (CLEOPATRA; 2012)	+	+	+	?	Partially	+	—	+	—	Intermediate
Blackwell et al, <sup>11</sup> Verma et al <sup>12</sup> (EMILIA; 2012)	+	?	+	+	—	+	+	+	—	Intermediate
Huober et al <sup>7</sup> (eLEcTRA; 2012)	?	?	—	Partially	?	+	?	? <sup>a</sup>	—	High
Kaufman et al <sup>6</sup> (TAnDEM; 2009)	+	?	+	+	—	+	Partially	+ <sup>b</sup>	—	High
Schwartzberg et al <sup>9</sup> (2010)	?	?	+	Partially	+	+	?	+ <sup>c</sup>	—	High
Andersson et al <sup>13</sup> (HERNATA; 2011)	+	+	+	+	?	+	Partially	+ <sup>d</sup>	—	Intermediate
Valero et al <sup>14</sup> (BCIRG 007; 2011)	+	+	+	+	—	+	+	+ <sup>e</sup>	—	Intermediate
Inoue et al <sup>15</sup> (JO17360; 2010)	+	+	Partially <sup>f</sup>	+	—	+	?	— <sup>g</sup>	—	Intermediate
Gelmon et al <sup>16</sup> (MA.31/GSK EGF108919; 2012)	?	?	?	+	?	Partially	Partially	+	—	?
Cameron et al, <sup>17</sup> Geyer et al <sup>18</sup> (EGF100151; 2010)	+	+	— <sup>h</sup>	+	Partially	Partially	?	+	—	High
Blackwell et al <sup>19,20</sup> (EGF104900; 2010, 2012)	?	?	?	+	—	+	+	+ <sup>i</sup>	—	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.

<sup>a</sup>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.

<sup>b</sup>For all patients who received  $\geq$  one dose of assigned study drug.

<sup>c</sup>Overall population included patients with HER2-negative disease.

<sup>d</sup>For efficacy. Safety analysis included all participants who received  $\geq$  one dose.

<sup>e</sup>Time to progression, response rate, response duration, and OS.

<sup>f</sup>Met target accrual, but this was  $<$  100 per arm.

<sup>g</sup>For safety. Modified ITT analysis included those patients in safety group, excluding one who did not meet eligibility.

<sup>h</sup>Did not meet target for OS.

<sup>i</sup>For efficacy analysis. Safety analysis included randomly assigned patients who received  $\geq$  one dose.

**Table 2. Efficacy Outcomes**

Study	Sample Size	PFS (months)	TTP (months)	OS (median)/Mortality		RR		Other Efficacy Results
				No.	%	No.	%	
Basejga et al <sup>10</sup> (CLEOPATRA; 2012)								
Pertuzumab, trastuzumab, and docetaxel	402	18.5 <sup>a,b</sup>		69	17.2		80.2	Investigator-assessed PFS: 18.5
Trastuzumab, docetaxel, and placebo	406	12.4 <sup>a,b</sup>		96 (deaths)	23.6		69.3	12.4
Summary statistic		HR for progression or death, 0.62		HR, 0.64			Difference, 10.8 <sup>c</sup>	HR, 0.65
95% CI		0.51 to 0.75		0.47 to 0.88			4.2 to 17.5	0.54 to 0.78
P		< .001		.005 <sup>d</sup>			.001 <sup>e</sup>	< .001
Blackwell et al, <sup>11</sup> Verma et al <sup>12</sup> (EMILIA; 2012)								Median duration of 2-year survival: response (investigator reviewed):
T-DM1	495	Median, 9.6 (265 events)		30.9 months <sup>f</sup>		85.2	43.6	12.6 months
Lapatinib plus capecitabine	496	Median, 6.4 (304 events)		25.1 months <sup>f</sup>		78.4	30.8	6.5 months
Summary statistic		Stratified HR, 0.650		0.68 <sup>g</sup>				
95% CI		0.55 to 0.77		0.55 to 0.85		82.0 to 88.5	38.6 to 48.6	59.3 to 70.2
P		< .001		< .001		74.6 to 82.3	26.3 to 35.7	45.9 to 57.7
Huober et al <sup>7</sup> (eLECTR; 2012)								Median duration of ORR (months):
Trastuzumab plus letrozole	26		14.1	NS		7 of 26	ORR, 27	11.4
Letrozole	31		3.3			4 of 31	ORR, 13	12.2
Letrozole alone (HER2 negative, hormone receptor positive)	35		15.2			4 of 35	ORR, 11 (HER2 positive v negative, letrozole alone)	16.5
Summary statistic		HR, 0.67 <sup>j</sup>		HR, 0.67 <sup>j</sup>			ORR: OR, 2.49 <sup>j,k</sup>	
95% CI		0.35 to 1.29		0.35 to 1.29			0.64 to 9.70	
P		.23		.23				

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**Table 2.** Efficacy Outcomes (continued)

Study	Sample Size	PFS (months)		TTP (months)		OS (median)/Mortality		1-Year Survival (%)		RR		Other Efficacy Results
		No.	%	No.	%	No.	%	No.	%	No.	%	
Kaufman et al <sup>8</sup> (TAnDEM; 2009)												
Trastuzumab plus anastrozole	103			4.8 (95% CI, 3.7 to 7)		28.5 months		20.3				PFS: TTP (population centrally confirmed as hormone receptor positive): 5.6 months
Anastrozole	104			2.4 (95% CI, 2 to 4.6)		23.9 months		6.8				5.6 months
Summary statistic				HR, 0.63								3.9 months
95% CI				0.47 to 0.84								HR, 0.62
P				.0016		.325		.18 (PR)				3.8 to 8.3
				< .001 (log rank)		NS						2.1 to 6.3
												.007
Schwartzberg et al <sup>9</sup> (2010)												
Lapatinib plus letrozole	111	8.2		12.4		33.3 months		28				CBR:
Placebo plus letrozole	108	3		15.3		32.3 months		15				
Summary statistic		HR, 0.71						OR, 0.4				OR, 0.4
95% CI		0.53 to 0.96						0.2 to 0.9				0.2 to 0.9
P		.019				NS		.021				.003
Andersson et al <sup>13</sup> (HERNATA; 2011)												
Trastuzumab plus docetaxel	143			12.4		35.7 months		123 of 143				
Trastuzumab plus vinorelbine	141			15.3		38.8 months		118 of 141				
Summary statistic				HR, 0.94								
95% CI				0.71 to 1.25		HR, 1.01						
P				.67		.98						
Valero et al <sup>14</sup> (BCIRG 007; 2011)												
Docetaxel, carboplatin, and trastuzumab	131			10.35 (95% CI, 9.36 to 12.12)		37.4 months (95% CI, 30.7 to 43.1)		72				Median duration of response: 9.43 months
Docetaxel and trastuzumab	132			11.07 (95% CI, 9.30 to 13.47)		37.1 months (95% CI, 32.6 to 43.6)		72				10.74 months
Summary statistic				HR, 0.914								
95% CI				0.694 to 1.203		HR, 1.015						
P				.57		.99						
Inoue et al <sup>15</sup> (JO17360; 2010)												
Trastuzumab followed by trastuzumab plus docetaxel	55	3.7				13		8 of 54				Median TTF: 114 days
Trastuzumab plus docetaxel	53	14.6				6		36 of 53				332 days

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Table 2. Efficacy Outcomes (continued)

Study	Sample Size	PFS (months)	TTP (months)	OS (median)/Mortality		RR		Other Efficacy Results
				No.	%	No.	%	
Summary statistic		HR, 4.24		HR, 4.72		HR, 2.81		1.77 to 4.47
95% CI		2.48 to 7.24		1.03 to 7.18				< .01
P		< .01		.04				
Gelmon et al <sup>16</sup> (MA.31/GSK EGF108919; 2012)								
Lapatinib plus taxane followed by lapatinib	318	8.8		NR				9 months
Trastuzumab plus taxane followed by trastuzumab	318	11.4		NR				13.7 months
Summary statistic		HR, 1.33		HR, 1.1				HR, 1.48
95% CI								1.15 to 1.92
P		.01		NS				.003
Cameron et al, <sup>17</sup> Geyer et al <sup>18</sup> (EGF100151; 2010)								
Lapatinib plus capecitabine (combination)	198	82 events		75 weeks <sup>l</sup>		23.7 (95% CI, 18 to 30.3)		27.1 weeks (6.2 months)
Capecitabine (monotherapy)	201	102 events		64.7 weeks <sup>l</sup>		13.9 (95% CI, 9.5 to 19.5)		18.6 weeks (4.3 months)
Summary statistic		HR, 0.55		HR, 0.87 <sup>17</sup>		OR, 2.0		HR, 0.57
95% CI		0.4 to 0.74		0.70 to 1.08		1.2 to 3.30		0.43 to 0.77
P		< .001		.206		.008		< .001
Blackwell et al <sup>19,20</sup> (EGF104900; 2010, 2012)								
Lapatinib alone	145	8.1 weeks		39.0 weeks		6.9 (95% CI, 5.9 to 16.4)		13
Lapatinib plus trastuzumab	146	12 weeks <sup>19</sup>		51.6 weeks <sup>19</sup>		10.3 (95% CI, 3.4 to 12.3)		28 <sup>b</sup>
Summary statistic		HR, 0.73		HR, 0.75		OR, 1.5		HR, 0.71
95% CI		0.57 to 0.93		0.53 to 1.07		0.6 to 3.9		0.52 to 0.98
P		.008		.106		.46		.027

Abbreviations: CBR, clinical benefit rate; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NR, not reached; NS, not significant; OR, objective response; ORR, objective response rate; OS, overall survival; PFS, progression-free survival; RR, response rate; T-DM1, trastuzumab emtansine; TTP, time to treatment failure; TTP, time to progression.

<sup>a</sup>Median PFS per prespecified subgroup of 88 of 808 patients who received adjuvant or neoadjuvant chemotherapy with trastuzumab.

<sup>b</sup>By independent review.

<sup>c</sup>ORR.

<sup>d</sup>Interim analysis did not meet stopping boundary at time of publication.

<sup>e</sup>OS did not cross stopping boundary; therefore, ORR was exploratory.

<sup>f</sup>Efficacy stopping boundary: HR, 0.73 or  $P = .0037$ .

<sup>g</sup>HR for death resulting from any cause.

<sup>h</sup> $P < .001$  in Verma et al.<sup>12</sup>

<sup>i</sup>Per German sites amendment; HER2-negative, hormone receptor-positive group received letrozole alone.

<sup>j</sup>Comparing two HER2-positive arms.

<sup>k</sup>For arm one v three: OR, 5.34; 95% CI, 1.83 to 15.58;  $P = .0024$ .

<sup>l</sup>Intention to treat.



Table 3. Data on AEs: One

Study	Sample Size	Diarrhea		First-Line Setting		Other GI <sup>a</sup>		Other AEs		Overall AEs	
		No.	%	No.	%	No.	%	No.	%	No.	%
Baselga et al <sup>10</sup> (CLEOPATRA; 2012)	402	32 <sup>b</sup>	7.9					Asthenia: <sup>b</sup> 10	2.5	2	2
Pertuzumab, trastuzumab, and docetaxel	406	20 <sup>b</sup>	5					Fatigue: <sup>b</sup> 9	2.2		
Trastuzumab, docetaxel, and placebo								13	3.3	2.5	2.5
								Dyspnea: <sup>b</sup> 4	1		
								8	2		
Blackwell et al, <sup>11</sup> Verma et al <sup>12</sup> (EMILIA; 2012) <sup>b</sup>								Fatigue:			
T-DM1	490 of 495	8	1.6	4	0.8			12	2.4	200 (1 resulting in death)	40.8
Lapatinib plus capecitabine	488 of 496 <sup>c</sup>	101	20.7	12	2.5			17	3.5	278 (4 resulting in death)	57
								Hand-foot syndrome: 0	0.0		
								80	16.4		
Huober et al <sup>7</sup> (eLECTRA; 2012)								Bone pain: <sup>b</sup>			
Trastuzumab plus letrozole	26	5	19	4	15			1	1	25	96
Letrozole	31	1	3	1	3			2	2	22	71
Letrozole alone (HER2 negative, hormone receptor positive)	35	1	3	1	3			2	2	28	80
Kaufman et al <sup>8</sup> (TAnDEM; 2009)								Nausea: <sup>b</sup>			
Trastuzumab plus anastrozole	103	1 <sup>b</sup>	1.0	1	1					Grade 3: 24	23.3
Anastrozole	104	0 <sup>b</sup>	0	0	0			Emesis: <sup>b</sup> 3	2.9	Grade 4: 5	4.9
								1	1	1	1.0
Schwartzberg et al <sup>9</sup> (2010)								Fatigue: <sup>b</sup> 4			
Lapatinib plus letrozole	113 of 111 <sup>d</sup>		7 <sup>a</sup>					0			
Letrozole plus placebo	106 of 108		0 <sup>a</sup>					Arthralgia: <sup>b</sup> 4			
								<1			

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**Table 3.** Data on AEs: One (continued)

Study	Sample Size	Diarrhea		Other GI <sup>a</sup>		Other AEs		Overall AEs	
		No.	%	No.	%	No.	%	No.	%
Andersson et al <sup>13</sup> (HERNATA; 2011)	143								
Trastuzumab plus docetaxel			8.6 <sup>b</sup>		3.6			81	
Trastuzumab plus vinorelbine	141		3.6 <sup>b</sup>		2.2			51	
			$P = .11$		$P = .72$				$P < .001$
Valero et al <sup>14</sup> (BCIRG 007; 2011)									
Docetaxel, carboplatin, and trastuzumab	131	13	9.9	5	3.8	1	0.8		
Docetaxel and trastuzumab	131	3	2.3	0	0	3	2.3		
				$P = .001$		$P < .001$			
				Vomiting: <sup>b</sup>					
				4	3				
				2	1.5				
				$P = .002$					
Inoue et al <sup>15</sup> (JO17360; 2010)									
Trastuzumab followed by trastuzumab plus docetaxel	55	NR		3	5			34 of 55 <sup>b</sup>	62
Trastuzumab plus docetaxel	53			1	2			46 of 53 <sup>b</sup>	87
Geimon et al <sup>16</sup> (MA.31/ GSK EGF108919; 2012) <sup>e</sup>									
Lapatinib plus taxane followed by lapatinib	313 of 318		19.3	1.9					
Trastuzumab plus taxane followed by trastuzumab	318		1.3	1					
		HR, NR		Vomiting:		Fatigue:			
				2.9		7.6			
				1.3		4.3			

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**Table 3.** Data on AEs: One (continued)

Study	Sample Size	Diarrhea		Other GI <sup>a</sup>		Other AEs		Overall AEs	
		No.	%	No.	%	No.	%	No.	%
Second-Line Setting									
Cameron et al, <sup>17</sup> Geyer et al <sup>18</sup> (EGF100151; 2010) <sup>f</sup>	207 of 207	7 <sup>g</sup>		0					47 events (24 patients); 6 deaths resulting from SAEs <sup>g</sup>
Lapatinib plus capecitabine (combination)									
Capecitabine (monotherapy)	191 of 201	5 <sup>g</sup>		3					57 events (28 patients); 6 deaths resulting from SAEs <sup>g</sup>
Lapatinib plus capecitabine (crossover)	36	1 <sup>g</sup>		1					11 events (6 patients) <sup>g</sup>
Nausea: <sup>g</sup>									
Vomiting: <sup>g</sup>									
Cough: <sup>i</sup>									
Blackwell et al <sup>19,20</sup> (EGF104900; 2010, 2012)									
Lapatinib alone	146	70	48 <sup>b,h</sup>	41	28	14	10	24 <sup>g</sup>	16
Lapatinib plus trastuzumab	149 (safety population)	90	60 <sup>b,h</sup>	41	28	8	5	38 <sup>1,9g</sup>	26 <sup>20</sup>
P = .03 <sup>i</sup>									
Nausea: <sup>i</sup>									
Vomiting: <sup>i</sup>									
Dermatitis acneliform: <sup>i</sup>									
Rash: <sup>i</sup>									
Cough: <sup>i</sup>									

Abbreviations: AE, adverse event; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; NR, not reached; SAE, serious adverse event; T-DM1, trastuzumab emtansine.

<sup>a</sup>For example, nausea.

<sup>b</sup>Grade ≥ 3.

<sup>c</sup>Grade 3 to 4 for safety population (ie, all patients ≥ one dose on study).

<sup>d</sup>Two patients randomly assigned to letrozole plus placebo arm actually received letrozole plus lapatinib; thus, safety population reports on 106 and 113 patients, respectively.

<sup>e</sup>Interim results.

<sup>f</sup>Results reported for > three reports.

<sup>g</sup>SAEs.

<sup>h</sup>In Blackwell et al<sup>20</sup> report, 7% in each arm.

<sup>i</sup>Reported in ≥ 10% of patients.

Table 4. Data on AEs: Two

Study	Sample Size	OOL		LVEF Decline		Cardiac AEs		Febrile Neutropenia		Other Hematologic AEs <sup>a</sup>	
		No.	%	No.	%	No.	%	No.	%	No.	%
First-Line Setting											
Baselga et al <sup>10</sup> (CLEOPATRA; 2012)		Declines ≥ 10% from baseline LVEF < 50%:									
Pertuzumab, trastuzumab, and docetaxel	402			3.8 <sup>b</sup>		5 <sup>b</sup>	1.2	56 <sup>b</sup>		13.8	
Trastuzumab, docetaxel, and placebo	406			6.6 <sup>b</sup>		11 <sup>b</sup>	2.8	30 <sup>b</sup>		7.6	
Blackwell et al, <sup>11</sup> Verma et al <sup>12</sup> (EMILIA; 2012)		FACT-B total:									
T-DM1	495	7.1 months (n = 450)		1.7	8					10	2
Lapatinib plus capecitabine	496	4.6 months (n = 445)		1.6	7					21	4.3
		HR, 0.80 95% CI, 0.67 to 0.95 P = .0121 <sup>c</sup>								Neutropenia: Thrombocytopenia: 63 12.9 1 0.2 <sup>12</sup>	
Huober et al <sup>7</sup> (eLEcTRA; 2012)		Mean change:									
Trastuzumab plus letrozole	26			7 <sup>b</sup>		No grade 4 cardiac AEs					
Letrozole	31			3 <sup>b</sup>							
Letrozole alone (HER2 negative, hormone receptor positive)	35			1 <sup>b</sup>							
Kaufman et al <sup>6</sup> (TAndEM; 2009)		≥ 15% from baseline to < 50%:									
Trastuzumab plus anastrozole	103				1					Grade 3 or 4:	
Anastrozole	104				0					2	2
Schwartzberg et al <sup>9</sup> (2010)		FACT-B total:									
Lapatinib plus letrozole	111 <sup>d</sup>	104	Mean, 99.3 (SD, 19.16)		3						
Placebo plus letrozole	108 <sup>d</sup>	96	Mean, 101.1 (SD, 19.31)		1 (asymptomatic) <sup>e</sup>						
		Subscale week 12 treatment group difference: 1.5-point difference in favor (BCS) 1.5-point difference in favor (SWB) <sup>g</sup> P < .05									

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Table 4. Data on AEs: Two (continued)

Study	Sample Size	OOL		LVEF Decline		Cardiac AEs		Febrile Neutropenia		Other Hematologic AEs <sup>a</sup>	
		No.	%	No.	%	No.	%	No.	%	No.	%
Andersson et al <sup>13</sup> (HERNATA; 2011)	143			Decline > 14% from baseline:						Leucopenia:	
Trastuzumab plus docetaxel				7.2						Grade 3, 35.2; grade 4, 2.2	Grade 3, 25.2; grade 4, 15.1
Trastuzumab plus vinorelbine	141			10.9						Grade 3, 10.1; grade 4, 0.7	Grade 3, 12.3; grade 4, 8.7
											$P < .001$
Valero et al <sup>14</sup> (BCIRG 007; 2011)				$P = .40$							$P < .001$
				LVEF decline > 15%:							Thrombocytopenia:
Docetaxel, carboplatin, and trastuzumab	131			All grades, 6.7				17	19		2 <sup>a</sup> 15.3
Docetaxel plus trastuzumab	131			5.5				16	12.2 <sup>a</sup>		3 <sup>a</sup> 2.3
											$P = NS$
Inoue et al <sup>15</sup> (JO17360; 2010)				Decrease to < 50%:							Leukopenia and neutropenia combined:
Trastuzumab followed by trastuzumab plus docetaxel	55			2	4.1		No CHF	2	4		20 36
Trastuzumab plus docetaxel	53			1	2			4	8		32 60
				Difference between baseline LVEF and lowest LVEF $\geq$ 10:							
				12	24.5						
				11	22						
Geimon et al <sup>16</sup> (MA.31/GSK EGF108919; 2012) <sup>h</sup>				Decline < 20% (greatest):							
Lapatinib plus taxane followed by lapatinib	318			Week 60, 28 of 42 (of 312)	67			17 (7 postamendment)			
Trastuzumab plus taxane followed by trastuzumab	318			Week 60, 50 of 70 (of 317)	71			7 (6 postamendment)			

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**Table 4.** Data on AEs: Two (continued)

Study	Sample Size	OOO		LVEF Decline		Cardiac AEs		Febrile Neutropenia		Other Hematologic AEs <sup>a,b</sup>	
		No.	%	No.	%	No.	%	No.	%	No.	%
Second-Line Setting											
Cameron et al, <sup>17</sup> Geyer et al <sup>18</sup> (EGF100151; 2010)	198			4 (asymptomatic)							
Lapatinib plus capecitabine (combination)	201			4 (asymptomatic)							
Blackwell et al <sup>19,20</sup> (EGF104900; 2010, 2012)	145	Time to deterioration: HR, 0.82 (95% CI, 0.56 to 1.20)		3		3 <sup>k</sup>					
Lapatinib alone	146	TOI: HR, 0.79 (95% CI, 0.55 to 1.14) BCS time to deterioration: HR, 1.02 (95% CI, 0.69 to 1.52)		8 <sup>k,l</sup>		10 (1 fatal event) <sup>20k</sup>					
Lapatinib plus trastuzumab											

Abbreviations: AE, adverse event; BCS, Breast Cancer Scale; CHF, congestive heart failure; FACT-B, Functional Assessment of Cancer Therapy–General; HR, hazard ratio; LVEF, left ventricular ejection fraction; NCI CTCAE, National Cancer Institute Common Terminology Criteria for Adverse Events; OOL, quality of life; SD, standard deviation; SWB, Spiritual Well-Being Scale; T-DM1, trastuzumab emtansine; TOI, Trial Outcome Index.

<sup>a</sup>For example, thrombocytopenia.  
<sup>b</sup>Mean LVEF change from baseline to minimum during treatment.  
<sup>c</sup>Median time to decrease of  $\geq 5$  points in FACT-B TOI score was delayed in T-DM1 group.  
<sup>d</sup>Two patients randomly assigned to letrozole plus placebo arm actually received letrozole plus lapatinib, thus, safety population reports on 106 and 113 patients, respectively.  
<sup>e</sup>LVEF equals space relative reduction in LVEF to  $\geq 20\%$  and below institutional normal limit.  
<sup>f</sup>Measuring social/family well-being.  
<sup>g</sup>All grades.  
<sup>h</sup>Interim results.  
<sup>i</sup>Protocol amended to require mandatory primary granulocyte colony-stimulating factor prophylaxis for those receiving lapatinib plus taxane followed by lapatinib (after first 189 patients randomly assigned).  
<sup>j</sup>NCI CTCAE (version 3.0) grade 3 or 4 left ventricular systolic dysfunction or  $\geq 20\%$  absolute decrease in LVEF relative to baseline value and below lower limit of institution.  
<sup>k</sup>NCI CTCAE (version 3.0) grade  $\geq 3$  left ventricular systolic dysfunction or decrease in left ventricular ejection fraction 20% relative to baseline value and below lower limit of institution.  
<sup>l</sup>Decrease of  $\geq 20\%$  from baseline and  $<$  lower limit of institution.

**Clinical interpretation.** Overall, HER2-targeted therapy in combination with chemotherapy in the first-line setting is associated with improvements in response rate, PFS, TTP, and OS when compared with chemotherapy alone. In trials of endocrine therapy, the addition of HER2-targeted therapy is associated with improvements in response rate and PFS but not in survival. These data support the use of HER2-targeted therapy in the first-line treatment of metastatic breast cancer. There are some contraindications to HER2-targeted therapy, as a result of its cardiovascular toxicity effects (Table 4). The single most important contraindication is a decreased left ventricular ejection fraction (LVEF) and/or clinical evidence of congestive heart failure arising from low LVEF. Among patients with congestive heart failure or low ejection fraction, the decision to use HER2-targeted therapy must be made on an individual basis, assessing the relative risks of cardiac dysfunction from a specific regimen versus disease progression. Therefore, the Expert Panel recommended that clinicians treat patients with clinical congestive heart failure or compromised LVEF on a case-by-case basis, assessing the relative risks of cardiac dysfunction versus disease progression.<sup>22</sup>

For select patients with HER2-positive and hormone receptor-positive (ER positive/PgR positive or negative) breast cancer, endocrine treatment with either trastuzumab or lapatinib or endocrine therapy alone may be an acceptable first-line treatment. Endocrine therapy alone is included as an option because the trials of endocrine therapy with or without HER2-targeted therapy did not demonstrate a survival advantage. This recommendation is discussed in Clinical Question 2/Recommendation 2.

### **Clinical Question 1.A.II**

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

**Recommendation 1.A.II.** 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.

**Literature review and analysis.** This recommendation is based on a body of evidence regarding second-line therapy, found both in the ASCO and CCO systematic reviews. The comparisons in three of the studies supporting this recommendation each included an intervention of an HER2-targeted therapy combination versus chemotherapy.<sup>17,23-27</sup> These three studies found a PFS or TTP and/or safety benefit for the HER2-targeted therapy combination arm.<sup>17,24-27</sup>

Two studies compared different HER-targeted therapies. The EMILIA (an open-label study of trastuzumab emtansine [T-DMI] v capecitabine + lapatinib in patients with HER2-positive locally advanced or metastatic breast cancer) study showed a statistically significant OS benefit for those receiving T-DMI over the combination of capecitabine and lapatinib.<sup>11,12</sup> The study of lapatinib alone versus lapatinib plus trastuzumab showed an OS benefit for lapatinib plus trastuzumab, but most of the survival benefit occurred postprogression, and the median number of prior therapies was four to five.<sup>19,20</sup> Recommendation 1.B.II and the Data Supplement provide further information.

**Clinical interpretation.** Overall, all of the studies showed that there is a benefit to continuing some form of HER2-targeted therapy in the second-line setting, either a combination of HER2-targeted therapy and chemotherapy, a combination of two HER2-targeted

therapies, or T-DMI. These were associated with improved outcomes. The EMILIA study showed both improvement in survival and a favorable toxicity profile for T-DMI when compared with capecitabine and lapatinib and confirmed the benefit of T-DMI in the second-line treatment of metastatic breast cancer.

### **Clinical Question 1.A.III**

Is HER2-targeted therapy recommended for all patients in the third-line setting and beyond?

**Recommendation 1.A.III.** 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.

**Literature review and analysis.** The lapatinib plus trastuzumab study<sup>20</sup> and the EMILIA study provide the evidence for this recommendation.<sup>11,12,19</sup> In neither of these studies were there survival differences based on the number of prior metastatic treatment regimens participants had received. In other studies, results were not presented by number of prior regimens.<sup>10,17,23-27</sup> The Data Supplement provides further information.

**Clinical interpretation.** The use of HER2-targeted therapies in the third-line setting and beyond was associated with improved PFS in subgroup analyses. However, neither of the two studies was specifically focused on this population; therefore, the data are not as strong as the data supporting the use of HER2-targeted therapies in the first- and second-line settings. A report from the TH3RESA (a study of T-DMI in comparison with treatment of physician's choice in patients with HER2-positive breast cancer who have received at least two prior regimens of HER2-directed therapy) study also showed an improvement in PFS with the use of T-DMI versus physician's choice for patients previously treated with both trastuzumab and lapatinib. However, the results of this study were presented after the ASCO literature search cutoff date and so were not formally considered as a basis for this recommendation (ClinicalTrials.gov identifier, NCT01419197).<sup>28</sup> The lapatinib plus trastuzumab study did include a heavily pretreated population and showed a benefit for continuing trastuzumab in combination with lapatinib after progression during previous trastuzumab-containing regimens. These data support the continuation of HER2-targeted therapy in the third-line setting and beyond.

### **Clinical Question 1.B**

Which HER2-targeted therapy (trastuzumab, lapatinib, pertuzumab, or T-DMI) with or without chemotherapy should be offered?

#### **Clinical Question 1.B.I**

What is the specific recommended regimen in the first-line setting?

**Recommendation 1.B.I.** 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.

**Literature review and analysis.** The panel reviewed data on pertuzumab, trastuzumab, lapatinib, and T-DMI in first-line-based regimens (combinations with hormone receptor-targeted drugs are

discussed later in this article). The recommendation for the pertuzumab, trastuzumab, and docetaxel combination is based on one phase III clinical trial: CLEOPATRA (Clinical Evaluation of Pertuzumab and Trastuzumab). This trial compared pertuzumab, trastuzumab, and docetaxel with trastuzumab plus docetaxel. If patients had previously received trastuzumab, an interval  $\geq 12$  months between neoadjuvant or adjuvant therapy and metastatic diagnosis was required (see Clinical Question 1.B.V.b).

The published benefits included an increase in PFS. There was also an increase in OS. The second interim analysis of CLEOPATRA found that the combination of pertuzumab, trastuzumab, and docetaxel was associated with an OS benefit (hazard ratio, 0.66;  $P < .001$ ); those data will be reviewed when published.<sup>29</sup> No increase in the risk of cardiac dysfunction was seen with addition of pertuzumab; LVEF declines were numerically less frequent in the pertuzumab arm, but the difference was not tested for statistical significance.<sup>10</sup> Because the CLEOPATRA regimen used a taxane, contraindications to the regimen included any contraindications to the use of a taxane, such as neuropathy, prior taxane hypersensitivity, and so on<sup>30</sup> (see drug labels for other contraindications). The Data Supplement provides further information.

**Clinical interpretation.** The Expert Panel reviewed evidence on the agents listed for first-line therapy. The combination of pertuzumab, trastuzumab, and docetaxel was more effective than trastuzumab plus docetaxel in CLEOPATRA, including for OS. The panel discussed whether the benefit of pertuzumab plus trastuzumab was likely to be limited to docetaxel versus paclitaxel. Although patients in CLEOPATRA were all treated with docetaxel, the panel felt that the use of paclitaxel with pertuzumab and trastuzumab was also reasonable, particularly for patients who might not be good candidates for docetaxel. Although it is likely that other chemotherapy agents can be combined safely and effectively with trastuzumab and pertuzumab, the use of alternative regimens would be supported only by limited data and should generally be avoided until additional data are available.

The panel discussed the use of T-DM1 in the first-line setting. Most of the participants in the EMILIA trial had received prior systemic therapy for metastatic breast cancer, although T-DM1 was first-line therapy for a minority of patients. The panel concluded that these data were insufficient to recommend T-DM1 in the first-line setting. Full accrual has been completed in a trial evaluating T-DM1 in the first-line setting; results are unavailable at this time. Clinical Question 1.B.V.a provides information on patients with a recurrence  $\leq 12$  months after adjuvant treatment.

### Clinical Question 1.B.II

What is the specific recommended regimen in the second-line setting?

**Recommendation 1.B.II.** If a patient's HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy, clinicians should recommend T-DM1 as a second-line treatment. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

**Literature review and analysis.** Lapatinib was approved by the FDA for the treatment of HER2-positive breast cancer in combination with capecitabine after an anthracycline, taxane, and trastuzumab. The combination of lapatinib and capecitabine was associated with a

longer time to progression than capecitabine alone, but not with a significant improvement in OS.<sup>17,19</sup>

EMILIA included participants who had received zero to  $>$  three prior regimens, comparing T-DM1, an antibody-drug conjugate,<sup>31</sup> with lapatinib plus capecitabine.<sup>11,12</sup> In the coprimary end points, OS and independently assessed median PFS were longer in the T-DM1 arm. One- and 2-year survival rates were also higher in the T-DM1 arm. Overall adverse events were lower with T-DM1 and higher in the control arm. In a subgroup analysis of PFS, the hazard ratio for second-line treatment favored T-DM1 (Verma et al<sup>12</sup> appendix). OS was not reported by subgroup. The Data Supplement provides further information.

**Clinical interpretation.** In EMILIA, the OS rates were statistically significantly higher in the T-DM1 arm than in the lapatinib plus capecitabine arm. In addition to improving survival, T-DM1 had a more favorable toxicity profile than the lapatinib and capecitabine combination, with lower rates of grade 3 to 4 toxicity and low rates of cardiac toxicity.

### Clinical Question 1.B.III

What is the specific recommended regimen in the third-line setting and beyond?

**Recommendation 1.B.III.a.** 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.

**Recommendation 1.B.III.b.** 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.

**Recommendation 1.B.III.c.** 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.

**Literature review and analysis.** The evidence for this recommendation is also primarily from the EMILIA study. Those who received T-DM1 in the third-line setting or beyond experienced a PFS benefit from T-DM1. There is no specific evidence about the use of pertuzumab, and the recommendation to offer a pertuzumab combination in the third-line setting is based on informal consensus; there are no randomized data evaluating pertuzumab in this setting. The Data Supplement provides further information. The lapatinib plus trastuzumab study is also relevant in that it showed an OS benefit for continuing trastuzumab (with lapatinib) after progression during a trastuzumab-containing regimen.<sup>19,20</sup>

**Clinical interpretation.** The Expert Panel considered the evidence for specific HER2-targeted regimens in the third-setting and beyond. There is strong evidence supporting the use of T-DM1 in the



third-line setting and beyond, because > 500 patients in EMILIA were treated in the third-line or greater setting. In contrast, the CLEOPATRA study of pertuzumab was limited to patients in the first-line setting.<sup>10</sup> A small phase II study<sup>32</sup> of pertuzumab plus trastuzumab in patients who had been previously treated with trastuzumab showed a response rate of 24% and a clinical benefit rate of 50%, indicating that pertuzumab has activity in this setting. The panel felt that there was insufficient evidence to make a strong recommendation for the use of pertuzumab in the third-setting and beyond. However, there was agreement that for patients who had never received pertuzumab, the use of this drug would be clinically appropriate. These patients would typically be those who received first- and second-line therapy before pertuzumab became available.

Many other combinations of HER2-targeted therapies can be used in the third-line setting and beyond, but no trials are available to provide head-to-head comparisons between the different combinations. Lapatinib plus capecitabine is an FDA-approved combination, but it has not been directly compared against other trastuzumab plus chemotherapy or trastuzumab plus lapatinib combinations and has not been shown to improve OS. Because of these limitations in the data, the panel was not able to recommend a particular HER2-targeted regimen in the third-line or greater setting, apart from T-DM1 in those not previously exposed to this agent. In patients with hormone receptor–positive disease, who have not received prior endocrine therapy in combination with HER2-targeted treatment, this approach can also be considered in the third-line setting.

#### **Clinical Question 1.B.IV**

What is the optimal timing, dose, schedule, and duration of treatment?

The a priori clinical question for this guideline included optimal timing, dose, and schedule, but there was no specific evidence to inform the issues on optimal timing or dose; therefore, the guideline will not provide recommendations on these. Some conclusions, however, were drawn regarding duration.

**Recommendation 1.B.IV.** 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.

**Literature review and analysis.** In the ASCO systematic review, there was a small trial by Inoue et al<sup>15</sup> of sequential trastuzumab followed by docetaxel after a patient's disease progressed versus concurrent first-line treatment with trastuzumab and docetaxel. The Inoue et al study found that first-line concurrent therapy with docetaxel and trastuzumab was associated with improved survival compared with sequential therapy. In virtually all of the first-line studies in the ASCO and CCO systematic reviews, the intervention was administered until unacceptable toxicity or disease progression. The systematic review for the CCO guideline on duration included two RCTs. One investigated capecitabine and trastuzumab versus capecitabine as second-line treatment.<sup>24</sup> The second reported initial results of the

lapatinib plus trastuzumab study.<sup>33</sup> (Please see second- and third-line treatment sections of the systematic review for updated results). In other studies found by ASCO, treatment was also administered until disease progression and/or unacceptable toxicity. The Data Supplement provides further information.

**Clinical interpretation.** The evidence from Inoue et al<sup>15</sup> suggests concurrent trastuzumab and chemotherapy is more beneficial in terms of OS, TTF, and PFS than adding chemotherapy at disease progression after initial therapy with single-agent trastuzumab. However, this study was small and therefore not definitive.<sup>15</sup>

In most trials, HER2-targeted therapy was administered until disease progression or until toxic adverse events caused the clinician and patient to decide to discontinue this therapy. There are insufficient data to make a single statement on when to stop administering HER-targeted therapy.<sup>34</sup> The recommendation for duration is based on the approach used in most of the relevant clinical trials, but it has not been formally studied in patients with HER2-positive breast cancer.

#### **Clinical Question 1.B.V**

How should any previous HER2 adjuvant therapy influence treatment?

##### **Clinical Question 1.B.V.a**

For patients with a recurrence  $\leq$  12 months after adjuvant treatment?

**Recommendation 1.B.V.a.** 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 (Recommendation 1.B.II). Type: evidence based. Evidence quality: intermediate. Strength of recommendation: moderate.

**Literature review and analysis.** In EMILIA, the eligibility criteria included a requirement that participants must have had progressive disease during metastatic treatment or within 6 months of adjuvant treatment. Potential participants were excluded if they had received prior T-DM1. Sixteen percent of participants in both arms had received prior trastuzumab treatment for early breast cancer only. In a subgroup analysis of PFS by prior trastuzumab treatment for metastatic breast cancer, both subgroups benefited from T-DM1 ( $\pm$  prior trastuzumab).<sup>12</sup> The Data Supplement provides further information.

**Clinical interpretation.** The Expert Panel discussed data to guide management of patients whose disease relapsed within 12 months of adjuvant therapy. Patients who had disease recurrence within 6 months of adjuvant therapy would have been eligible for EMILIA but not eligible for CLEOPATRA.<sup>10-12</sup> Patients who had disease recurrence between 6 and 12 months would not have been eligible for either EMILIA or CLEOPATRA. Because of the short interval between relapse and adjuvant therapy, which likely would have included both trastuzumab and a taxane, the panel felt that standard second-line therapy with T-DM1 would be most appropriate, recognizing the limitations of the data.

##### **Clinical Question 1.B.V.b**

For patients with a recurrence > 12 months after adjuvant treatment?

**Recommendation 1.B.V.b.** If a patient finished trastuzumab-based adjuvant treatment > 12 months before recurrence, clinicians should follow the first-line HER2-targeted therapy–based treatment recommendations (Recommendation 1.B.I). Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

**Literature review and analysis.** In CLEOPATRA, if patients had received previous trastuzumab, the study required a  $\geq$  12-month interval between neoadjuvant or adjuvant trastuzumab and metastatic diagnosis. In a prespecified subgroup analysis among patients who had received prior trastuzumab, the median independently assessed PFS was 16.9 months versus 10.4 months for patients treated with pertuzumab, trastuzumab, and docetaxel versus trastuzumab plus docetaxel, respectively.<sup>10</sup> The Data Supplement provides further information.

**Clinical interpretation.** In the pertuzumab trial, the entrance criteria included those who had received prior adjuvant treatment; participants in this subgroup had a longer PFS by 6.5 months. However, these participants represented only 12% of those in the pertuzumab arm. The panel acknowledges that additional research is needed observe the effects of pertuzumab in this population. An ongoing trial (MARIANNE [a study of T-DM1 plus pertuzumab/pertuzumab placebo v trastuzumab plus a taxane in patients with metastatic breast cancer]; T-DM1 plus pertuzumab/pertuzumab placebo versus trastuzumab plus a taxane in patients with metastatic breast cancer) may provide additional results about patients who have received prior trastuzumab treatment (ClinicalTrials.gov identifier, NCT01120184). Overall, because patients whose disease relapsed > 12 months from adjuvant treatment would have been eligible for the CLEOPATRA trial, the panel felt that these patients should receive standard first-line treatment (Clinical Question 1.B.I).

## CLINICAL QUESTION 2

For patients with HER2-positive advanced breast cancer that is also ER positive ( $\pm$  PgR positive), does ER/PgR status influence decisions about the following:

### Clinical Question 2.A

What is the most appropriate first-line therapy for patients with HER2-positive, ER-positive (PgR positive or negative) advanced breast cancer?

If a patient's cancer is hormone receptor positive and HER2 positive, clinicians may recommend either:

**Recommendation 2.A.I.** HER2-targeted therapy plus chemotherapy. Type: evidence based. Evidence quality: high. Strength of recommendation: strong.

**Recommendation 2.A.II.** Endocrine therapy plus trastuzumab or lapatinib (in selected cases). Type: evidence based. Evidence quality: high. Strength of recommendation: moderate.

**Recommendation 2.A.III.** Endocrine therapy alone (in selected cases; see Recommendation 2.C). Type: evidence based. Evidence quality: intermediate. Strength of recommendation: weak.

**Literature review and analysis.** There is no evidence that the response of patients with HER2-positive advanced breast cancer to HER2-targeted therapy differs by ER/PgR status. The ASCO systematic review found three first-line trials comparing an HER2-targeted agent plus endocrine therapy versus endocrine therapy alone. eLECTRA (study of the efficacy and safety of letrozole combined with trastuzumab) was a small, first-line trial comparing trastuzumab plus

letrozole versus letrozole. Eligibility included no prior treatment for metastatic breast cancer or locally advanced breast cancer. The trial did not reach its target enrollment of 300 patients (92 actual participants) and closed prematurely.<sup>7</sup> The median TTP was 14.1 months in the trastuzumab plus letrozole arm versus 3.3 months in the letrozole alone arm, but this was not statistically significant.<sup>7</sup> Schwartzberg et al<sup>9</sup> conducted a study of lapatinib plus letrozole versus letrozole. The TAnDEM (Trastuzumab and Anastrozole Directed Against ER-Positive HER2-Positive Mammary Carcinoma) study compared anastrozole with trastuzumab plus anastrozole. In these two studies, the combination arm showed longer PFS.<sup>8,9</sup> The difference in OS was not statistically significant in any of the three studies.<sup>7-9</sup> Patients with ER-positive breast cancer were also included in the first-line chemotherapy trials, such as CLEOPATRA, which showed an OS benefit for chemotherapy and HER2-targeted therapy combinations. The Data Supplement provides further information.

**Clinical interpretation.** Clinicians should not determine HER2-targeted therapy options based solely on the ER/PgR status of a patient's cancer. Although the clinician may discuss using endocrine therapy with or without HER2-targeted therapy, the majority of patients will still receive chemotherapy plus HER2-targeted therapy. No studies have directly compared endocrine therapy plus HER2-targeted therapy with chemotherapy plus HER2-targeted therapy. The studies of chemotherapy with HER2-targeted therapy have shown an OS benefit, but the studies of endocrine therapy with HER2-targeted therapy have not. Given the improved toxicity profile of endocrine therapy versus chemotherapy, some clinicians may offer first-line endocrine therapy with or without HER2-targeted therapy. Currently, there are no methods for identifying patients who would benefit from combined therapy versus endocrine therapy alone. Although there seems to be no OS benefit to adding HER2-targeted therapy to endocrine therapy, two of studies did show a PFS benefit for the combination therapy groups. Therefore, the Expert Panel chose to list these combined regimens as an option. Endocrine therapy alone in the first-line setting is discussed in Recommendation 2.C.

### Clinical Question 2.B

If a clinician plans to offer endocrine therapy at some point during a woman's treatment, what is the appropriate sequencing?

**Recommendation 2.B.** If the patient has started with a 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.

**Clinical interpretation.** There are insufficient data to inform this recommendation; therefore, the Expert Panel made an informal consensus recommendation. No data exist to guide the clinician on when to offer endocrine therapy. However, the panel felt that most patients with HER2-positive and ER-positive/PgR-positive or -negative metastatic breast cancer should receive a course of endocrine therapy at some point in their treatment. Most of the members of the Expert Panel favored starting with chemotherapy and HER2 therapy combinations in the majority of patients, given that these regimens have been associated with an OS benefit. When chemotherapy is discontinued, clinicians may recommend patients start endocrine therapy, typically administered

in conjunction with HER2-targeted therapy. Alternatively, endocrine therapy may also be started at the time of subsequent disease progression.

### Clinical Question 2.C

Can clinicians offer first-line endocrine therapy? If so, should it always be in combination with HER2-targeted therapy?

**Recommendation 2.C.** 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.

**Clinical interpretation.** There are insufficient data to inform this recommendation; therefore, the Expert Panel made an informal consensus recommendation. For patients with HER2-positive and ER-positive/PgR-positive or -negative disease who are not good candidates for chemotherapy or for those who wish to avoid the toxicity of chemotherapy, initial therapy with endocrine agents is a reasonable option. In most circumstances, endocrine therapy should be administered with HER2-targeted therapy, because the PFS for patients treated with endocrine therapy alone is only 2 to 3 months.<sup>8,9</sup> However, given that the addition of HER2 therapy to endocrine therapy does not improve OS, select patients may be treated with endocrine therapy alone. Patients who have low-volume disease, a long disease-free interval, indolent disease, significant comorbidities, or a preference to avoid intravenous medication or additional toxicity would be the most appropriate candidates for endocrine therapy alone.

## PATIENT AND CLINICIAN COMMUNICATION

This section is a summary of an extended discussion in the Data Supplement and 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 2009 version of the ASCO stage IV non-small-cell lung cancer guideline<sup>35</sup> and to literature on risk communication for patients with cancer.<sup>36</sup> A patient who is newly diagnosed with metastatic disease versus one for whom first- and/or second-line treatment or greater has failed will likely to 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, referring to patients to <http://www.cancer.net> links and psychosocial support, and introducing concepts of concurrent palliative and anti-tumor therapies.<sup>35,37-39</sup>

Research on discussing specific issues with patients with HER2-positive metastatic disease is still needed. Teams should be prepared to present the statistics 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 Data Supplement 7.

## HEALTH DISPARITIES

Health disparities between patients with breast cancer according to race/ethnicity, age, insurance status, geographic location, education, and other factors are well documented.<sup>40</sup> A brief literature search, not part of the systematic review, was conducted to find literature addressing health disparities specific to patients with HER2-positive metastatic breast cancer. The results found a paucity of currently available reports of outcome/risk by HER2 status/HER2-targeted therapy analyzed by these factors.<sup>40</sup> According to some studies, there are not large (although some suggest modest) differences in the prevalence of HER2 positivity between women with breast cancer of different races/ethnicities. The variation by race is smaller among those with HER2-positive breast cancer than for some other subtypes.<sup>41-44</sup> HER2 positivity is not necessarily associated with worse treatment outcomes among African American compared with non-African American patients.<sup>45</sup> However, high-quality data on patients with HER2-positive metastatic disease are still needed to reach conclusions related to outcomes based on ethnicity. Therefore, health disparities may be similar to those faced by patients with metastatic breast cancer generally.

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.<sup>46-49</sup> 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.

## 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.<sup>50</sup>

### 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 agents in this guideline are FDA approved and available; however, cost is an issue that may be appropriate to discuss with patients, because copayments and other expenses are insurance dependent and/or financial assistance may be available. Unfortunately, there are parts of the country where access to a medical oncologist might be limited, and because of reimbursement issues, some smaller practices are referring elsewhere for expensive treatments. There is also the issue of the uninsured who do not qualify for Medicaid or other financial assistance. ASCO provides resources on cost of care for your patient. Most practicing oncologists in the United States have used trastuzumab and lapatinib and are starting to gain experience with pertuzumab and T-DM1. As with all new treatments, diffusion in the community must occur in time.

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 *Journal of Clinical Oncology*.

### LIMITATIONS OF THE RESEARCH

Limitations of the research on patients with HER2-positive metastatic breast cancer include a lack of confirmatory trials for new agents, limited data on second-line treatment, and limited data on third-line treatment and beyond. The Expert Panel awaits the publication of a report on the ongoing TH3RESA trial. There are also limited data on the best ways to provide treatment with endocrine therapy/HER2-targeted therapy, on the best sequencing, timing, and duration, and on the best strategy when the failure of adjuvant treatment occurs between 6 and 12 months. There are limited data on pertuzumab regi-

mens other than in CLEOPATRA, especially in patients who have received adjuvant trastuzumab.

### FUTURE DIRECTIONS

Research is needed in the areas discussed in the previous section, as well as in factors that predispose resistance to first-line metastatic breast cancer HER2-targeted therapy regimens; research is also needed to address the reasons for the within-in study heterogeneity of patients with HER2-positive metastatic breast cancer in TTP. High-quality data on patients with HER2-positive metastatic disease regarding age, race/ethnicity, and other potential health disparities are also needed.<sup>51,52</sup>

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

This guideline, as well as its companion on treating brain metastases in patients with HER2-positive metastatic breast cancer, is available at <http://jco.ascopubs.org>. 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/guidelines/treatHER2pos](http://www.asco.org/guidelines/treatHER2pos). Patient information is available at <http://www.cancer.net>.

### AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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

Member	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
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
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	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
Naren Ramakrishna, MD, PhD	University of Florida Health Cancer Center at Orlando Health, Orlando, FL	Radiation oncology

NOTE. American Society of Clinical Oncology staff: Sarah Temin, MSPH.

Abbreviations: HER2, human epidermal growth factor receptor 2; UPMC, University of Pittsburgh Medical Center.