Systemic Therapy for Advanced Human Epidermal Growth Factor Receptor 2–Positive Breast Cancer

ASCO Guideline Update

Giordano et al.
Overview

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Background & Methodology
Introduction

• The purpose of this guideline update\(^1\) 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 HER2-positive metastatic breast cancer in 2014 and updated the guidelines in 2018.\(^2\)

• This current update assesses whether the 2018 recommendations remain valid and provides oncologists and other clinicians with current recommendations regarding the treatment of patients with HER2-positive metastatic breast cancer.

• The companion ASCO clinical practice guideline on management of advanced HER2–positive breast cancer and brain metastases accompanies this guideline update.\(^3\)
ASCO Guideline Development Methodology

• The ASCO Evidence Based Medicine Committee (EBMC) guideline process includes:
  ▪ a systematic literature review by ASCO guidelines staff
  ▪ an expert panel provides critical review and evidence interpretation to inform guideline recommendations
  ▪ final guideline approval by ASCO EBMC

• The full ASCO Guideline methodology manual can be found at: www.asco.org/guideline-methodology
Clinical Question

This clinical practice guideline addresses one overarching guideline question:

- What is the optimal medical therapy for advanced HER2-positive breast cancer, specifically HER2-targeted therapy, either alone or in combination with chemotherapy and/or endocrine therapy?
Target Population and Audience

Target Population

• Individuals with advanced HER2-positive breast cancer

Target Audience

• Medical oncologists, radiation oncologists, surgeons, oncology nurses, patients, and caregivers
Summary of Recommendations
Summary of Recommendations

**Recommendation 1.0**

- Clinicians should recommend HER2-targeted therapy-based combinations for first-line treatment, except for highly selected patients with ER+ or PgR+ and HER2- positive disease for whom clinicians may use endocrine therapy alone.

<table>
<thead>
<tr>
<th>Evidence Quality</th>
<th>Strength of Recommendation</th>
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<tbody>
<tr>
<td>High</td>
<td>Strong</td>
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**Recommendation 1.1**

- Clinicians should recommend the combination of trastuzumab, pertuzumab, and a taxane for first-line treatment, unless the patient has a contraindication to taxanes.

<table>
<thead>
<tr>
<th>Evidence Quality</th>
<th>Strength of Recommendation</th>
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<tbody>
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Summary of Recommendations

Recommendation 2.0

• 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.

Recommendation 2.1

• If a patient’s HER2-positive advanced breast cancer has progressed during or after first-line HER2-targeted therapy (and the patient has not received T-Dxd), clinicians should recommend T-Dxd as a second-line treatment.
Summary of Recommendations

**Recommendation 3.0**

- 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-line HER2-targeted therapy-based treatment.

*Overall, there are a lack of head-to-head trials, therefore there is insufficient evidence to recommend one regimen over another. The patient and clinician should discuss differences in treatment schedules, routes, toxicities during the decision-making process. Options include the recommendations in the following slides:*
Summary of Recommendations

Recommendation 3.1

• If a patient’s HER2-positive advanced breast cancer has progressed during or after second-line or greater HER2-targeted treatment and the patient has already received pertuzumab and TDxd (if a patient has not received pertuzumab, clinicians may offer pertuzumab), clinicians should recommend third-line or greater HER2-targeted therapy-based treatment.

Recommendation 3.1.1

• If a patient has not received T-DM1 in second-line, should offer T-DM1 regimen

Evidence

- Evidence-based benefits outweigh harms

Evidence Quality

- High

Strength of Recommendation

- Strong
Summary of Recommendations

**Recommendation 3.1.2**
- May offer tucatinib combined with trastuzumab and capecitabine

**Recommendation 3.1.3**
- May offer T-Dxd
Summary of Recommendations

Recommendation 3.1.4
• May offer neratinib combined with capecitabine

Recommendation 3.1.5
• May offer lapatinib and trastuzumab
Summary of Recommendations

**Recommendation 3.1.6**
- May offer lapatinib and capecitabine

**Recommendation 3.1.7**
- May offer other combinations of chemotherapy and trastuzumab
Summary of Recommendations

**Recommendation 3.1.8**

- May offer margetuximab plus chemotherapy

**Evidence Quality**

<table>
<thead>
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**Evidence-based**

<table>
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**Recommendation 3.1.9**

- If a patient has not received pertuzumab, clinicians may offer pertuzumab

**Evidence Quality**

<table>
<thead>
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<th>Strength of Recommendation</th>
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<table>
<thead>
<tr>
<th>Evidence Quality</th>
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<tbody>
<tr>
<td>Insufficient</td>
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Summary of Recommendations

Recommendation 3.2.0

• May offer hormonal therapy (in patients with ER+ and/or PgR+ disease)

Evidence-based benefits outweigh harms

Evidence Quality Strength of Recommendation
Moderate Weak

Recommendation 3.2.1

• May offer abemaciclib combined with trastuzumab and fulvestrant

Evidence-based benefits outweigh harms

Evidence Quality Strength of Recommendation
Moderate Weak
Summary of Recommendations

Recommendation 4.0

• If a patient is receiving HER2-targeted therapy and chemotherapy combinations, the chemotherapy should continue for approximately 4-6 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.
Summary of Recommendations

Recommendation 5.0

• If a patient finished trastuzumab-based adjuvant treatment ≤ 12 months before recurrence, clinicians should follow the second-line HER2-targeted therapy-based treatment recommendations.

Evidence Quality: Intermediate
Strength of Recommendation: Moderate

Recommendation 5.1

• If a patient finished trastuzumab-based adjuvant treatment >12 months before recurrence, clinicians should follow the first-line HER2-targeted therapy-based treatment recommendations.

Evidence Quality: High
Strength of Recommendation: Strong
Summary of Recommendations

Recommendation 6.0

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

Recommendation 6.0.1

• HER2-targeted therapy plus chemotherapy

Recommendation 6.0.2

• Endocrine therapy plus trastuzumab or lapatinib (in selected cases)

Recommendation 6.0.3

• Endocrine therapy alone (in selected cases)
Summary of Recommendations

Recommendation 7.0

• 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.
Summary of Recommendations

Recommendation 8.0

• In special circumstances, such as low disease burden, the presence of co-morbidities (contradictions to HER2-targeted therapy such as congestive heart failure), and/or the presence of a long disease free-interval, clinicians may offer first-line endocrine therapy alone.

• Qualifying Statement: Although the clinician may discuss using endocrine therapy with or without HER2-targeted, the majority of patients should still receive chemotherapy plus HER2-targeted therapy.
Discussion
Biosimilars

- An FDA-approved biosimilar can be an appropriate substitute for trastuzumab. More information regarding the use of biosimilars is discussed in the ASCO statement: Biosimilars in Medications in Oncology.  
- With five biosimilars available for trastuzumab (FDA approved between December 2017 - June 2019 – trastuzumab-qyyp; trastuzumab-dttb; trastuzumab-pkrb; trastuzumab-anns; (trastuzumab-dkst) it is necessary that information about biosimilars be developed and communicated to patients. 
- Ideally, this communication should come from the physician and reinforced with other educational materials.
- Clinicians will also benefit from educational information about biosimilars in order to inform and field patient questions in a knowledgeable manner to foster patient confidence.
- Establishing these communication protocols is important for both patients newly diagnosed with metastatic cancer, and those who previously received a protocol with trastuzumab.
## Cost Implications

### Centers for Medicare & Medicaid Services Reimbursement of Injections

<table>
<thead>
<tr>
<th>Agent, Route</th>
<th>Payment Limit/HCPCS Code</th>
<th>Dosagea</th>
<th>Dose and Scheduleb</th>
<th>Cost for One Cycle (USD; drug only)c</th>
</tr>
</thead>
<tbody>
<tr>
<td>Injection</td>
<td>Medicare part B</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Ado-T-DM1 IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Trastuzumab excl biosimilar IV</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Herceptin hylecta subcutaneous</td>
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<tr>
<td>Fam-trastuzumab deruxtecan-nxki IV</td>
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<td>Margetuximab-cmkb IV</td>
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<tr>
<td>Pertuzumab IV</td>
<td></td>
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<tr>
<td>Pertuzumab IV</td>
<td></td>
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</table>

Abbreviations: BSA, body surface area; HCPCS, Healthcare Common Procedures Coding System; IV, intravenous; T-DM1, trastuzumab emtansine; USD, US dollars

a Payment limit effective January 1, 2022.
b Assumes weight of 84 kg, height 168.3 cm, and BSA of 2 (average of females and males ≥ 20 years; females ≥ 20 years, all racial and ethnic groups [US sample], mean weight 77.5 kg, mean height 161.3 cm; BSA 1.86 using Mosteller formula; males ≥ 20 years, all racial and ethnic groups [US sample], mean weight 90.6 kg, mean height 175.3 cm; BSA 2.1 using Mosteller formula).c Does not include administration costs or facility charges.
## Cost Implications
### Oral Drug Cost Table

<table>
<thead>
<tr>
<th>Oral Agents (with additional agents in regimen)</th>
<th>Strength</th>
<th>Brand/ Generic</th>
<th>Dose and Schedulea (Cycled every 21 days)</th>
<th>Wholesale Acquisition Cost $ (per tablet)</th>
<th>Monthly Medicare Insuredb (Initial copay $2,500 - $3,500, then 5% of Total Drug Cost; $ per tablet)</th>
<th># Tabs per cycle</th>
<th>Cost for One Cycle (Drug Only) c WAC $</th>
<th>Medicare $</th>
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<tbody>
<tr>
<td>Capecitabine (w/ tucatinib, trastuzumab)</td>
<td>500 mg</td>
<td>Generic</td>
<td>1000 mg/m² twice daily on days 1-14</td>
<td>5.2:39</td>
<td>0.26-1.95</td>
<td>112</td>
<td>582.4 - 4,368</td>
<td>29.12 - 218.4</td>
</tr>
<tr>
<td></td>
<td>500 mg</td>
<td>Brand</td>
<td></td>
<td>43.38</td>
<td>2.17</td>
<td>112</td>
<td>4,858.56</td>
<td>243.04</td>
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<tr>
<td>Capecitabine (w/ trastuzumab)</td>
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<td>Generic</td>
<td>1000-1250 mg/m² twice daily on days 1-14</td>
<td>5.2:39</td>
<td>0.26-1.95</td>
<td>112-140</td>
<td>582.4 - 4,368</td>
<td>29.12 - 218.4</td>
</tr>
<tr>
<td></td>
<td>500 mg</td>
<td>Brand</td>
<td></td>
<td>43.38</td>
<td>2.17</td>
<td>112-140</td>
<td>4,858.56 - 6,073.2</td>
<td>243.04 - 303.8</td>
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<tr>
<td>Capecitabine (w/ lapatinib)</td>
<td>500 mg</td>
<td>Generic</td>
<td>1000 mg/m² twice daily on days 1-14</td>
<td>5.2:39</td>
<td>0.26-1.95</td>
<td>112</td>
<td>582.4 - 4,368</td>
<td>29.12 - 218.4</td>
</tr>
<tr>
<td></td>
<td>500 mg</td>
<td>Brand</td>
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<tr>
<td>Capecitabine (w/ margetuximab)</td>
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<td>Generic</td>
<td>1000 mg/m² twice daily on days 1-14</td>
<td>5.2:39</td>
<td>0.26-1.95</td>
<td>112</td>
<td>582.4 - 4,368</td>
<td>29.12 - 218.4</td>
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<tr>
<td></td>
<td>500 mg</td>
<td>Brand</td>
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<td>43.38</td>
<td>2.17</td>
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<td>Capecitabine (w/ neratinib)</td>
<td>500 mg</td>
<td>Generic</td>
<td>750 mg/m² twice daily on days 1-14</td>
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<td>0.26-1.95</td>
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<td>436.8 - 3,276</td>
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<tr>
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<td>Brand</td>
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<td>2.17</td>
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<td>Lapatinib (w/ capecitabine)</td>
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<td>Generic</td>
<td>1250 mg daily on days 1-21</td>
<td>48.11</td>
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<td>5,051.55</td>
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<td></td>
<td>250 mg</td>
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<td>53.46</td>
<td>2.67</td>
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<td>Lapatinib (w/ trastuzumab)</td>
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<td>1000 mg daily on days 1-21</td>
<td>48.11</td>
<td>2.41</td>
<td>84</td>
<td>4,041.24</td>
<td>202.44</td>
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<tr>
<td></td>
<td>250 mg</td>
<td>Brand</td>
<td></td>
<td>53.46</td>
<td>2.67</td>
<td>84</td>
<td>4,490.64</td>
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<td>Neratinib (w/ capecitabine)</td>
<td>40 mg</td>
<td>Brand</td>
<td>240 mg daily on days 1-21</td>
<td>102.8</td>
<td>5.14</td>
<td>126</td>
<td>12,952.8</td>
<td>647.64</td>
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<tr>
<td>Tucatinib (w/ capecitabine, trastuzumab)</td>
<td>150 mg</td>
<td>Brand</td>
<td>300 mg twice daily on days 1-21</td>
<td>172.61</td>
<td>8.63</td>
<td>84</td>
<td>14,499.24</td>
<td>724.92</td>
</tr>
</tbody>
</table>

NOTE. $: WAC or list price is 80% of AWP.°
Abbreviations: AWP, average wholesale report; BSA, body surface area; USD, US dollars; w/, with; WAC, wholesale acquisition cost.

- Assumess weight of 84 kg, height 168.3 cm, and BSA of 2 (average of females and males ≥ 20 years; females ≥ 20 years, all racial and ethnic groups [US sample], mean weight 77.5 kg, mean height 161.3 cm; BSA 1.86 using Mosteller formula; males ≥ 20 years, all racial and ethnic groups [US sample], mean weight 90.6 kg, mean height 175.3 cm; BSA 2.1 using Mosteller formula).7
- Medicare: the typical catastrophic coverage for tier 5 drugs is approximately 5% of drug cost (or WAC), once out-of-pocket cost is met.9
- Does not include dispensing fees.

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Limitations of the Research and Future Research

• Limitations in the evidence included:
  - Insufficient information on receiving agents that patients were not previously exposed to if disease relapsed within ≤12 months.
  - Insufficient data to inform the management of patients whose disease relapses or progresses after adjuvant T-DM1.

• The Expert Panel awaits:
  - Studies on route of administration in the metastatic setting
  - Research on other antibody-drug conjugates
  - Research to inform the best sequencing of anti-HER2 agents in third-line and beyond
  - The results of pyrotinib studies
  - Published results of ongoing studies, such as KATE3 and DESTINY 03
  - Validated diagnostics for CD16A genotypes

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

• More information, including a supplement and clinical tools and resources, is available at www.asco.org/breast-cancer-guidelines

• Patient information is available at www.cancer.net
# Guideline Panel Members

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

- ASCO, American Society of Clinical Oncology
- EBMC, Evidence Based Medicine Committee
- ER+, estrogen receptor-positive
- FDA, US Food and Drug Administration
- HER2, human epidermal growth factor receptor 2
- PgR+, progesterone receptor-positive
- T-DM1, trastuzumab emtansine
- T-Dxd, trastuzumab deruxtecan
References


8. IBM Corporation, IMB® Micromedex® Red Book®, Cambridge, MA, 2020

Disclaimer

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