Systemic Therapy for Patients With Advanced HER2-Positive Breast Cancer
Introduction

• ~15% of patients with breast cancer have tumors that overexpress the HER2 protein, and these patients can benefit from HER2-targeted therapies

• Several new agents FDA-approved for the treatment of patients with HER2-positive metastatic breast cancer

• Recommendations on management of brain metastases in patients with HER2-positive breast cancer are in a companion guideline
Guideline Methodology: Systematic Review

- The Expert Panel completed a systematic review and analysis of the medical literature through October 2012
  - Medline
- Limited portion of evidence base, specifically regarding trastuzumab, was gathered from systematic reviews produced by Cancer Care Ontario (CCO) on use of:
  - Trastuzumab
  - Trastuzumab beyond disease progression
Overarching Clinical Questions

(1) What are the optimal treatments for patients with HER2-positive advanced breast cancer in the first-, second-, third-lines and beyond?

(2) What are the optimal timing, dose, schedule, and duration of treatment?

(3) How should any previous HER2 adjuvant therapy influence treatment?

(4) How does ER/PgR status influence decisions about treatment of patients with HER2-positive and hormone receptor-positive advanced breast cancer
CQs & Recommendations

Question 1.A. Is HER2-targeted therapy recommended for all patients with HER2-positive advanced breast cancer 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 estrogen receptor-positive (ER+) or progesterone receptor-positive (PgR+) 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)
CQs & Recommendations

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, then clinicians should recommend second-line HER2-targeted therapy-based treatment. (Type: Evidence-based; Evidence Quality: High, Strength of Recommendation: Strong)
CQs & Recommendations

Question 1.A.III. Is HER2-targeted therapy recommended for all patients 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)
Recommendations

Question 1.B. If HER2-targeted therapy is recommended, then which HER2-targeted therapy (trastuzumab, lapatinib, pertuzumab, and/or trastuzumab emtansine [TDM-1]) ± chemotherapy should be offered?

Question 1.B.I. In first-line?

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)
CQs & Recommendations

Question 1. B.II. In second-line?

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)
Recommendations

Question 1. B.III. In third or greater-line?
Recommendation I.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 TDM-1, clinicians should offer TDM-1. (Type: Evidence-based; Evidence Quality: High, Strength of Recommendation: Strong)

Recommendation I.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)

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Recommendation 1.B.III., continued
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 TDM-1, clinicians should recommend third- or greater-line HER2-targeted therapy-based treatment. Options include lapatinib and capecitabine, as well as other combinations of chemotherapy and trastuzumab, lapatinib and trastuzumab, or hormonal therapy (in patients with ER+ and/or PgR+ disease). There is insufficient evidence to recommend one regimen over another. (Type: Informal consensus; Evidence Quality: Insufficient, Strength of Recommendation: Weak)
Recommendations

Question 1.B.IV. What are the optimal timing, dose, schedule, and duration of treatment?

Recommendation 1.B.IV. 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. (Type: Evidence-based; Evidence Quality: Intermediate, Strength of Recommendation: Moderate)
Recommendations

Question 1.B.V. How should any previous HER2 adjuvant therapy influence treatment?

Question 1.B.V.a. If there is a recurrence ≤12 months?

Recommendation 1.B.V.a. If a patient finished trastuzumab-based adjuvant treatment ≤12 months prior to 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)
Recommendations

Question 1.B.V.b. How should any previous HER2 adjuvant therapy influence treatment?, continued

Question 1. 1.B.V.b. If there is a recurrence >12 months?

Recommendation 1.B.V.b. If a patient finished trastuzumab-based adjuvant treatment >12 months prior to 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)
Clinical Question 2.A. What is the most appropriate first-line therapy if a patient’s cancer is hormone receptor-positive and HER2-positive:

Recommendation 2.A. Clinicians may recommend either:
2.A.I. HER2-targeted therapy plus chemotherapy (Type: Evidence-based; Evidence Quality: **High**, Strength of Recommendation: **Strong**), OR

2.A.II. Endocrine therapy plus trastuzumab or lapatinib (in selected cases) (Type: Evidence-based; Evidence Quality: **High**, Strength of Recommendation: **Moderate**), OR

2.A.III. Endocrine therapy alone (in selected cases; see Recommendation 2.C.) (Type: Evidence-based; Evidence Quality: **Intermediate**, Strength of Recommendation: **Weak**)

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Clinical Question 2.B. If a clinician plans to offer endocrine therapy at some point during the 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 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, the presence of co-morbidities (contraindications 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. (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.
Patient and Clinician Communication

• Present the statistics in this guideline in a format tailored to the patient/caregiver’s learning style. Discussions with patients should include key subjects, such as:

• Explanation of metastatic breast cancer and the objectives of treatment (prolonging life versus curative)
• Treatment options, including clinical trials, with potential benefits, side effects and risks
• The availability of supportive care
• Importance of considering chronic conditions such as CHF in choosing treatments
• Explanation of treatment failure and lines of treatment, including for patients with brain metastases
• The multiple members of the clinical team who may implement these recommendations, including oncology nurses, radiation oncologists, neurosurgeons, palliative care clinicians, psychosocial professionals, etc.
Limitations

• Limitations of the research include:
  • A lack of confirmatory trials for new agents
  • Limited data for treatment in second-line
  • Very limited data for treatment in third-line and beyond
  • The best ways to provide treatment with endocrine therapy/HER2-targeted therapy
  • The best sequencing, timing, and duration
  • The best strategy when the failure of adjuvant treatment occurs between six and 12 months
  • Pertuzumab regimens other than in CLEOPATRA, especially with patients who had adjuvant trastuzumab
Future Directions

• The Expert Panel recommended future directions in research including:
  • Factors that predispose resistance to first-line metastatic breast cancer HER2-targeted therapy regiments
  • Addressing the reasons for the within-in study heterogeneity of patients with HER2-positive metastatic breast cancer in time to progression
  • Age, race/ethnicity, and other potential health disparities
The Bottom Line

- **Interventions**
  - HER2-targeted therapy, chemotherapy, endocrine therapy

- **Target Population**
  - Individuals with advanced HER2-positive breast cancer

- **Target Audience**
  - Medical, surgical, and radiation oncologists; oncology nurses and physician assistants; and patients/caregivers

- **Methods**
  - Systematic review and analysis of the medical literature

- **Additional Information**
  - Recommendations and summary of the literature and analysis in guideline
  - Guideline on patients with HER2-positive breast cancer and brain metastases available at [www.asco.org/guidelines/her2brainmets](http://www.asco.org/guidelines/her2brainmets)
Additional Resources

• This guideline, as well as its companion on treating brain metastases in patients with HER2+ MBC, is available at jco.ascopubs.org
  • www.asco.org/guidelines/breast-cancer

• The guideline, a methodology supplement, data supplements, and other resources are available at www.asco.org/guidelines/treatHER2pos

• The patient guide is also available at http://www.cancer.net
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