TITLE: Systemic Therapy for Patients with Advanced HER2-Positive Breast Cancer: American Society of Clinical Oncology Clinical Practice Guideline

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METHODOLOGY SUPPLEMENT:

OVERVIEW
Practice guidelines are systematically developed statements that assist practitioners and patients in making decisions about care. Attributes of good guidelines include validity, reliability, reproducibility, clinical applicability, flexibility, clarity, multidisciplinary process, review of evidence, and documentation. Guidelines may be useful in producing better care and decreasing cost. Specifically, utilization of clinical guidelines may provide:

1. Improvements in outcomes
2. Improvements in medical practice
3. A means for minimizing inappropriate practice variation
4. Decision support tools for practitioners
5. Points of reference for medical orientation and education
6. Criteria for self-evaluation
7. Indicators and criteria for external quality review
8. Assistance with reimbursement and coverage decisions
9. Criteria for use in credentialing decisions
10. Identification of areas where future research is needed

Panel Composition
The ASCO Clinical Practice Guidelines Committee (CPGC) and the ASCO Breast Cancer Guideline Advisory Group (GAG) convened an Expert Panel with multidisciplinary representation in medical oncology, radiation oncology, and community oncology, the Practice Guidelines Implementation Network, and patient/advocacy representation. The Expert Panel was led by two Co-Chairs who had the primary responsibility for the development and timely completion of the guideline. The Panel had one face-to-face meeting and one webinar. The Co-Chairs and ASCO staff prepared a draft guideline for review and rating by the Expert Panel. The Expert Panel members are listed in Appendix Table A1 (online only).

Guideline Development Process
The Expert Panel met on several occasions and corresponded frequently through email; progress on guideline development was driven primarily by the Co-Chairs and ASCO staff. The purpose of the Panel meetings was for members to contribute content, provide critical review, interpret evidence, and finalize the guideline recommendations based upon the consideration of the evidence. All members of the Expert Panel participated in the preparation of the draft guideline document, which was then disseminated for external review and submitted to the Journal of Clinical Oncology (JCO) for peer review and publication. All ASCO guidelines are reviewed and approved by the ASCO CPGC prior to publication.

Revision Dates
The Co-Chairs and two Committee members designated by the Co-Chairs will determine the need for guideline updates or revisions based on periodic examination of the literature. When appropriate, that Committee will recommend revised guidelines to the CPGC for review and approval.

Systematic Literature Review
ASCO guidelines are based on systematic reviews of the literature. A protocol for each systematic review defines parameters for a targeted literature search. Additional parameters include relevant study designs, literature sources, types of reports, and pre-specified inclusion
and exclusion criteria for literature identified. The protocol for this guideline was reviewed and approved by the CPGC’s Methodology Subcommittee and Breast Cancer GAG.

**Literature Search Strategy**
PubMed and the Cochrane Collaboration Library electronic databases were searched for evidence reporting on outcomes of interest. Primary outcomes of interest were overall survival, progression-free survival, adverse events, and quality of life. Secondary outcomes of interest included overall response rates. A Cancer Care Ontario (CCO) systematic review on trastuzumab addressed several of the same questions as this guideline with a systemic literature search with a closing date parameter of 2009. Therefore, searches of PubMed for clinical questions on trastuzumab were searched to complement and update that CCO’s date parameters (ASCO search: January 1, 2009 through October 4, 2012). Searches for clinical questions on other HER2-targeted therapy-containing regimens were searched from 1966 through October 4, 2012 (clinical questions not [or partially] addressed in the CCO guidelines). The ASCO clinical questions regarded treatment included in first-, second-, third- and greater-line settings, including time and duration and the role of hormone receptor status.

Searches of ASCO Annual Meeting abstracts (2011, 2012), European Society of Medical Oncology (ESMO) (2010), and the San Antonio Breast Cancer Symposium (2010, 2011) were conducted for all clinical questions. Reference lists of seminal papers and recent review articles were scanned for additional citations. The literature search strategy and search results are available in Data Supplements 2 and 3 respectively.

**Data extraction**
Literature search results were reviewed and deemed appropriate for full text review by an ASCO staff member, in consultation with the Expert Panel Co-Chairs. Data were extracted by one reviewer and subsequently checked for accuracy through an audit of the data by another ASCO staff member. Disagreements were resolved through discussion and consultation with the Co-Chairs if necessary.

**DEVELOPMENT OF RECOMMENDATIONS**

The guideline recommendations were crafted, in part, using the GuideLines Into DEcision Support (GLIDES) methodology and accompanying BRIDGE-Wiz™ software. This method helps guideline panels systematically develop clear, translatable, and implementable recommendations using natural language, based on the evidence and assessment of its quality, to increase usability for end users. The process incorporates distilling the actions involved, identifying who will carry them out, to whom, under what circumstances, and clarifying if and how end users can carry out the actions consistently. This process helps the Panel focus the discussion, avoid using unnecessary and/or ambiguous language, and clearly state its intentions.

**BRIDGE-Wiz Steps with Examples**

<table>
<thead>
<tr>
<th>Step #</th>
<th>Step</th>
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<tbody>
<tr>
<td>1</td>
<td>Choose action type</td>
</tr>
<tr>
<td></td>
<td>Example: Prescribe</td>
</tr>
<tr>
<td>Step</td>
<td>Task</td>
</tr>
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</table>
| 2    | Based on the action type, select verb  
**Example:** Administer AND use |
| 3    | Administer and use **what?** (verb object) [n.b., users can add more than one verb and object(s). The verb "consider" is disallowed.]  
**Example:** administer combination of two cytotoxic drugs AND use platinum combinations |
| 4    | Check if the actions are specific and unambiguously written (Executability)  
**Example:** Modify if necessary |
| 5    | Define **When** (under what conditions)  
**Example:** Patients who have not previously been treated for metastatic NSCLC |
| 6    | Add other conditions with AND or OR  
**Example:** AND Have ECOG PS 0 or 1 AND do not have contraindications to platinum agents |
| 7    | Check if users will be able to consistently the circumstances (Decidability) – modify if needed  
**Example:** Add language if necessary, e.g. list contraindications |
| 8    | Enter potential **benefits** for each Action (What are the anticipated benefits of administering two cytotoxic drugs IF patients have not been previously treated for metastatic NSCLC AND don’t have contraindications to platinum drugs)  
**Example:** improvement in radiologic response rate, improvement in overall survival |
| 9    | Enter potential **risks, harms and costs** for each Action (What are the anticipated risks, harms and costs of administering two cytotoxic drugs IF patients have not been previously treated for metastatic NSCLC AND Have ECOG PS 0 or 1 AND don’t have contraindications to platinum drugs)  
**Example:** List toxicities |
| 10   | Judge **benefit-harms balance** (Options: Equilibrium, Preponderance of Risks, Harms, Costs, Preponderance of Benefits)  
**Example:** Preponderance of Benefits |
| 11   | Select **Aggregate Evidence Quality** (High, Intermediate, Low, or Insufficient)  
**High** |
| 12   | BRIDGE-Wiz proposes **recommendation strength** (options: Strong, Moderate, Weak) and term for the **level of obligation** (options: Must, Should, May)  
**Example 1:** Based on the Quality of Evidence **High** AND **Preponderance of Benefit**  
this key action statement can have a Recommendation Strength of **Strong**.  
**Example 2:** Based on this, the level of obligation should be Must or Should (choose one): **Should** |
| 13   | Define **who**  
**Oncology clinicians** |
| 14   | Choose a recommendation style from 4 options (n.b., can edit)  
**Example:** If patients have not received treatment yet for metastatic NSCLC AND have an ECOG PS 0 or 1  
Then  
Oncology clinicians should administer combination of two cytotoxic drugs (Evidence quality: High; Recommendation strength: Strong) AND oncologists should use platinum combinations, except if patients have contraindications. (Evidence quality: High; Recommendation strength: Strong)
BRIDGE-Wiz generates an Evidence Profile, includes “Key Action Statement,” “Aggregate Evidence Quality,” “Benefits,” “Risk, Harm, Cost,” and “Benefit-Harm Assessment” for each “Action” and places to insert “Value Judgments,” “Intentional Vagueness,” “Role of Patient Preferences,” “Exclusions”, and “Notes”

Guide for Types of Recommendations

<table>
<thead>
<tr>
<th>Type of Recommendation</th>
<th>Definition</th>
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<tbody>
<tr>
<td>Evidence based</td>
<td>There was sufficient evidence from published studies to inform a recommendation to guide clinical practice.</td>
</tr>
<tr>
<td>Formal consensus</td>
<td>The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. Therefore, the Expert Panel used a formal consensus process to reach this recommendation, which is considered the best current guidance for practice. The Panel may choose to provide a rating for the strength of the recommendation (i.e., “strong,” “moderate,” or “weak”). The results of the formal consensus process are summarized in the guideline and reported in the Data Supplement.</td>
</tr>
<tr>
<td>Informal consensus</td>
<td>The available evidence was deemed insufficient to inform a recommendation to guide clinical practice. The recommendation is considered the best current guidance for practice, based on informal consensus of the Expert Panel. The Panel agreed that a formal consensus process was not necessary for reasons described in the literature review and discussion. The Panel may choose to provide a rating for the strength of the recommendation (i.e., “strong,” “moderate,” or “weak”).</td>
</tr>
<tr>
<td>No recommendation</td>
<td>There is insufficient evidence, confidence, or agreement to provide a recommendation to guide clinical practice at this time. The Panel deemed the available evidence as insufficient and concluded it was unlikely that a formal consensus process would achieve the level of agreement needed for a recommendation.</td>
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Guide for Strength of Recommendations

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<tr>
<th>Rating for Strength of Recommendation</th>
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<tr>
<td>Strong</td>
<td>There is high confidence that the recommendation reflects best practice. This is based on (1) strong evidence for a true net effect (e.g., benefits exceed harms); (2) consistent results, with no or minor exceptions; (3) minor or no concerns about study quality; and/or (4) the extent of panelists’ agreement. Other compelling considerations (discussed in the guideline’s literature review and analyses) may also warrant a strong recommendation.</td>
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### Guide for Rating Strength of Evidence

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<tr>
<td>High</td>
<td>High confidence that the available evidence reflects the true magnitude and direction of the net effect (i.e., balance of benefits vs harms) and that further research is very unlikely to change either the magnitude or direction of this net effect.</td>
</tr>
<tr>
<td>Intermediate</td>
<td>Moderate confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research is unlikely to alter the direction of the net effect; however, it might alter the magnitude of the net effect.</td>
</tr>
<tr>
<td>Low</td>
<td>Low confidence that the available evidence reflects the true magnitude and direction of the net effect. Further research may change either the magnitude and/or direction this net effect.</td>
</tr>
<tr>
<td>Insufficient</td>
<td>Evidence is insufficient to discern the true magnitude and direction of the net effect. Further research may better inform the topic. The use of the consensus opinion of experts is reasonable to inform outcomes related to the topic.</td>
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### Guide for Rating of Potential for Bias

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<th>Rating of Potential for Bias</th>
<th>Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials</th>
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<tr>
<td>Low risk</td>
<td>No major features in the study that risk biased results, and none of the limitations are thought to decrease the validity of the conclusions. The study avoids problems such as failure to apply true randomization, selection of a population unrepresentative of the target patients, high dropout rates, and no intention-to-treat analysis; and key study features</td>
</tr>
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### Ratings of Potential for Bias

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<thead>
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<th>Definitions for Rating Potential for Risk of Bias in Randomized Controlled Trials</th>
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<tr>
<td>Intermediate</td>
<td>The study is susceptible to some bias, but flaws are not sufficient to invalidate the results. Enough of the items introduce some uncertainty about the validity of the conclusions. The study does not meet all the criteria required for a rating of good quality, but no flaw is likely to cause major bias. The study may be missing information, making it difficult to assess limitations and potential problems.</td>
</tr>
<tr>
<td>High risk</td>
<td>There are significant flaws that imply biases of various types that may invalidate the results. Several of the items introduce serious uncertainty about the validity of the conclusions. The study has serious errors in design, analysis, or reporting; large amounts of missing information; or discrepancies in reporting.</td>
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### References

