Introduction

- Gastroesophageal adenocarcinoma (GEA) is estimated to represent up to 43,280 cancer cases in the US in 2016,¹ and represents the eighth (esophageal) and fifth (stomach) most common cancers worldwide.²

- In 2010, results of an open-label, international, phase 3 randomized controlled trial (Trastuzumab for Gastric Cancer, ToGA), showed that the anti-HER2 humanized monoclonal antibody trastuzumab (Herceptin) statistically significantly prolonged overall survival compared with chemotherapy alone in patients with HER2–positive advanced GEA.³

- In 2007, a joint expert panel convened by the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP) met to develop guidelines for when and how to test for HER2 in patients with breast cancer, which is amplified and/or overexpressed in up to 30% of cases.⁴

- Because there are important distinct differences in HER2 expression, scoring, and outcomes in GEA relative to breast carcinoma, the need for HER2 guidelines (that include critical clinical and laboratory considerations) was recognized.


©American Society of Clinical Oncology 2016. All rights reserved.
CAP/ASCP/ASCO Guideline Development Methodology

The process for this guideline included:

• a systematic literature review
• an expert panel provided critical review and evidence interpretation to inform guideline recommendations
• final guideline approval by the CAP independent review panel, ASCP Special Review Panel, and ASCO CPGC

The full guideline methodology supplement can be found at:
www.asco.org/her2-gastric-guideline
Clinical Questions

What is the optimal testing algorithm for the assessment of HER2 status in patients with GEA?

What strategies can help ensure optimal performance, interpretation, and reporting of established assays in patients with GEA?
Target Population and Audience

Target Population
Patients with Gastroesophageal Adenocarcinoma

Target Audience
Medical and surgical oncologists; oncology nurses and physician assistants; pathologists; general practitioners; and patients

www.asco.org/her2-gastric-guideline
©American Society of Clinical Oncology 2016. All rights reserved.
Summary of Recommendations

CLINICAL QUESTION 1
What is the optimal testing algorithm for the assessment of HER2 status in patients with GEA?

Recommendation 1.1
In patients with advanced GEA who are potential candidates for HER2 targeted therapy, the treating clinician should request HER2 testing on tumor tissue (Type: Evidence based; Quality of evidence: High; Strength of recommendation: Strong).

Recommendation 1.2
Treating clinicians or pathologists should request HER2 testing on tumor tissue in the biopsy or resection specimens (primary or metastasis) preferably prior to the initiation of trastuzumab therapy if such specimens are available and adequate. HER2 testing on FNA specimens (cell blocks) is an acceptable alternative (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Recommendation/Moderate).

Recommendation 1.3
Treating clinicians should offer combination chemotherapy and HER2-targeted therapy as the initial treatment for appropriate patients with HER2 positive tumors who have advanced GEA (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

www.asco.org/her2-gastric-guideline
©American Society of Clinical Oncology 2016. All rights reserved.
CLINICAL QUESTION 2
What strategies can help ensure optimal performance, interpretation, and reporting of established assays in patients with GEA?

Recommendation 2.1
Laboratories/pathologists must specify the antibodies and probes used for the test and ensure that assays are appropriately validated for HER2 IHC and ISH on GEA specimens (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

Recommendation 2.2
When GEA HER2 status is being evaluated, laboratories/pathologists should perform/order IHC testing first followed by ISH when IHC result is 2+ (equivocal). Positive (3+) or negative (0 or 1+) HER2 IHC results do not require further ISH testing (Type: Evidence based; Quality of evidence: High; Strength of recommendation: Strong).

Recommendation 2.3
Pathologists should use the Ruschoff/Hofmann method in scoring HER2 IHC and ISH results for GEA (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).
Recommendation 2.4

Pathologists should select the tissue block with the areas of lowest grade tumor morphology in biopsy and resection specimens. More than one tissue block may be selected if different morphologic patterns are present (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Recommendation/Moderate).

Recommendation 2.5

Laboratories should report HER2 test results in GEA specimens in accordance with the CAP biomarker “Template for Reporting Results of HER2 (ERBB2) Biomarker Testing of Specimens From Patients With Adenocarcinoma of the Stomach or Esophagogastric Junction” (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).
Recommendation 2.6
Pathologists should identify areas of invasive adenocarcinoma and also mark areas with strongest intensity of HER2 expression by IHC in GEA specimen for subsequent ISH scoring when required
(Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

Recommendation 2.7
Laboratories must incorporate GEA HER2 testing methods into their overall laboratory quality improvement program, establishing appropriate quality improvement monitors as needed to assure consistent performance in all steps of the testing and reporting process. In particular, laboratories performing GEA HER2 testing should participate in a formal proficiency testing program, if available, or an alternative proficiency assurance activity (Type: Evidence based; Quality of evidence: Moderate/Intermediate; Strength of recommendation: Strong).

Recommendation 2.8
There is insufficient evidence to recommend for or against genomic testing in GEA patients at this time.
HER2 immunochemistry showing representative cases for scoring.

(A) Negative 0: No reactivity, specifically no membranous reactivity is seen in any of the tumor cells. Any cytoplasmic staining is disregarded for scoring purposes; (B) Negative 1+: Tumor cells with faint/barely perceptible membranous staining; (C) Equivocal 2+: Tumor cells with weak to moderate complete, basolateral and lateral membranous staining. Columnar cells that are sectioned tangentially tend to show a complete membranous staining pattern; (D) Positive 3+: Tumor cells with a strong complete, basolateral and lateral membranous reactivity. Also note that cells showing a complete membranous staining pattern are often tangentially sectioned columnar cells.
**HER2** and CEP 17 fluorescence in situ hybridization (FISH) shows scores of representative cases

(A) Not amplified: Ratio 1.0. Mean number of HER2 signals per cell is 1.9; mean number of CEP 17 signals per cell is 1.8; (B) Not amplified: Ratio 1.3. Mean number of HER2 signals per cell is 3.4; mean number of CEP 17 signals per cell is 2.7. Segmental duplication (or polysomy) likely accounts for signal numbers over 2 per cell; (C) Amplified: Ratio 3.0. Mean number of HER2 signals per cell is 5.2; mean number of CEP 17 signals per cell is 1.7.
Conclusion

• GEA continues to be a major healthcare burden throughout the world.

• Advanced GEA that is not amenable to effective local therapy remains incurable and patients have limited therapeutic options.

• Other than HER2, there is no biomarker available for selection of therapy for patients with advanced GEA.

• Trastuzumab is the only approved HER2-directed therapy that has resulted in modest but statistically significant prolongation of overall survival of HER2 positive GEA patients.
Additional Resources

More information, including a Data Supplement, a Methodology Supplement, slide sets, and clinical tools and resources, is available at

www.asco.org/her2-gastric-guideline

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

<table>
<thead>
<tr>
<th>Member</th>
<th>Affiliation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angela Bartley, co-chair</td>
<td>St. Joseph Mercy Hospital, Ann Arbor, MI</td>
</tr>
<tr>
<td>Mary Kay Washington, co-chair</td>
<td>Vanderbilt-Ingram Cancer Center, Nashville, TN</td>
</tr>
<tr>
<td>Jaffer Ajani, co-chair</td>
<td>MD Anderson Cancer Center, Houston, TX</td>
</tr>
<tr>
<td>Sanjay Kakar</td>
<td>University of California, San Francisco, CA</td>
</tr>
<tr>
<td>Laura Tang</td>
<td>Memorial Sloan Kettering Cancer Center, New York, NY</td>
</tr>
<tr>
<td>Megan Troxell</td>
<td>Oregon Health &amp; Science University, Portland, OR</td>
</tr>
<tr>
<td>Catherine Streutker</td>
<td>St. Michael's Hospital, University of Toronto, Toronto, Canada</td>
</tr>
<tr>
<td>Dhanpat Jain</td>
<td>Yale University School of Medicine, New Haven, CT</td>
</tr>
<tr>
<td>Margaret L. Gulley</td>
<td>University of North Carolina, Chapel Hill, NC</td>
</tr>
<tr>
<td>Helen J Mackay</td>
<td>Princess Margaret Cancer Centre, Toronto, Canada</td>
</tr>
<tr>
<td>Alfredo Carrato</td>
<td>Ramony Cajal University Hospital, Madrid, Spain</td>
</tr>
<tr>
<td>Al B. Benson III</td>
<td>Northwestern University, Chicago, IL</td>
</tr>
</tbody>
</table>

www.asco.org/her2-gastric-guideline
©American Society of Clinical Oncology 2016. All rights reserved.
References


Disclaimer

The Clinical Practice Guidelines and other guidance published herein are provided by the American Society of Clinical Oncology, Inc. (ASCO) to assist providers in clinical decision making. The information herein should not be relied upon 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 therein and is not applicable to other interventions, diseases, or stages of diseases. This information does not mandate any particular course of medical care. Further, the information is not intended to substitute for the independent professional judgment of the treating provider, as the information does not account for individual variation among patients. Recommendations reflect high, moderate, or low confidence that the recommendation reflects the net effect of a given course of action. The use of words like “must,” “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.

www.asco.org/her2-gastric-guideline

©American Society of Clinical Oncology 2016. All rights reserved.