ToGA: Trastuzumab with Standard Chemotherapy for HER2-Positive Advanced Gastric Cancer (GC)
OVERVIEW OF ACTIVITY

Each year, thousands of clinicians and basic scientists sojourn to the American Society of Clinical Oncology (ASCO) Annual Meeting to learn about recent clinical advances that yield alterations in state-of-the-art management for all tumor types. Attracting more than 30,000 attendees from every corner of the globe to both unveil and digest the latest research, ASCO is unmatched in attendance and clinical relevance. Results presented from ongoing trials lead to the emergence of new therapeutic agents and changes in the indications for existing treatments across all cancer medicine. Despite the importance of the conference, the demands of routine practice often limit the amount of time oncology clinicians can realistically dedicate to travel and learning. To bridge the gap between research and patient care, this CME activity will deliver a serial review of the key presentations from the ASCO Annual Meeting and expert perspectives on how these new evidence-based concepts can be applied to routine clinical care. This activity will assist medical oncologists and other cancer clinicians in the formulation of optimal clinical management strategies for patients with diverse forms of cancer.

LEARNING OBJECTIVES

- Identify patients with inoperable, locally advanced or metastatic HER2-positive GC who may benefit from the addition of trastuzumab to a standard fluoropyrimidine/cisplatin-containing chemotherapy regimen.
- Recognize the unique factors that affect assessment and interpretation of HER2 expression in gastric tumors.

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Last review date: July 2009
Expiration date: July 2010
Click to go directly to our ToGA slides or the ASCO reports on ofatumumab.

In addition to having a really cool name, Eric Van Cutsem has been a major contributor to GI cancer research, and his ASCO 2008 plenary presentation on K-ras and cetuximab instantly changed the standard of care in colon cancer. For my money, Dr Van Cutsem should have been back on the plenary stage this year presenting his paradigm shaking ToGA trial data set, which demonstrated a 26 percent relative reduction in mortality when trastuzumab was added to platinum/fluoropyrimidine therapy as first-line treatment for metastatic HER2-positive gastric cancer.

Translational scientists have claimed for years that molecular targets are found in a variety of primary tumors, but until ToGA, the concept was mainly theoretical. This Belgian-led study that included patients from pretty much everywhere except North America, has clearly changed that as a breast cancer-like 22 percent of screened gastric tumors were found to be HER2-positive. What this means for nonprotocol treatment and future adjuvant trials is now being hotly debated.

Click here to see our ToGA slides.

Oncologic antibodies like trastuzumab have only been around for a decade or so, but for part 2 of this issue of 5 Minute Journal Club we examine a second-generation antibody, ofatumumab. Two ASCO 2009 data sets on this new, fully human anti-CD20 antibody show robust and encouraging antitumor activity in patients with CLL who received prior R-chemo and in some cases, alemtuzumab. It remains for ongoing and planned Phase III trials to determine if five years from now we will still be talking about FCR and R-CHOP or if FCO, O-CHOP and a bunch of other new letter regimens will provide better outcomes for patients.
See our slides on the ASCO reports on ofatumumab, and watch for our next 5MJC issue focused on pemetrexed as “early second-line” (also called maintenance) therapy in non-small cell lung cancer and tissue biomarker findings from the IPASS study demonstrating that patients with EGFR mutations being treated for first-line mets do better on an EGFR TKI than on chemo.

Neil Love, MD
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Miami, Florida
ToGA: Trastuzumab with Standard Chemotherapy for HER2-Positive Advanced Gastric Cancer (GC)

Presentations discussed in this issue:


Slides from the presentations and excerpts from a related interview with Charles D Blanke, MD (June 11, 2009)
**Introduction**

- Chemotherapy improves survival compared to best supportive care by approximately 6 months in patients with advanced GC (JCO 2006;24:2903)
- Combination chemotherapy is superior to monotherapy (JCO 2006;24:2903)
- There is no universally accepted standard treatment for advanced GC
  - Fluoropyrimidine/platinum-based chemotherapy considered a reference regimen + the addition of anthracycline or docetaxel
  - Biologics under investigation
- ~22% of patients with advanced GC have HER2-positive disease (Bang ASCO 2009;4556)
- Trastuzumab is active against GC cell lines in vitro and in vivo
- **Current study objectives**:  
  - Evaluate the addition of trastuzumab to fluoropyrimidine/cisplatin in patients with HER2-positive advanced GC

Source: Van Cutsem E et al. ASCO 2009; Abstract LBA4509.

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**ToGA Trial Design**  
(N = 584)

**Eligibility**

HER2-positive, inoperable, locally advanced or metastatic GC

**Randomization (R)**

- FC  
  Fluoropyrimidine (F) (5-FU or capecitabine at investigator discretion) + Cisplatin (C)
- FCT  
  F + C + Trastuzumab (T)

**5-FU** = 800 mg/m²/day continuous infusion d1-5 q3w x 6  
**Capecitabine** = 1000 mg/m² bid d1-14 q3w x 6  
**Cisplatin** = 80 mg/m² q3w x 6  
**Trastuzumab** = 8 mg/kg loading dose ➔ 6 mg/kg q3w until PD

Source: Van Cutsem E et al. ASCO 2009; Abstract LBA4509.
### Results: Efficacy

<table>
<thead>
<tr>
<th></th>
<th>FC (n = 290)</th>
<th>FC + T (n = 294)</th>
<th>HR</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall survival</td>
<td>11.1 mos</td>
<td>13.8 mos</td>
<td>0.74</td>
<td>0.0046</td>
</tr>
<tr>
<td>Progression-free survival</td>
<td>5.5 mos</td>
<td>6.7 mos</td>
<td>0.71</td>
<td>0.0002</td>
</tr>
<tr>
<td>Overall response rate (CR + PR)</td>
<td>34.5%</td>
<td>47.3%</td>
<td>--</td>
<td>0.0017</td>
</tr>
<tr>
<td>Complete response (CR)</td>
<td>2.4%</td>
<td>5.4%</td>
<td>--</td>
<td>0.0599</td>
</tr>
<tr>
<td>Partial response (PR)</td>
<td>32.1%</td>
<td>41.8%</td>
<td>--</td>
<td>0.0145</td>
</tr>
</tbody>
</table>

Source: Van Cutsem E et al. ASCO 2009; Abstract LBA4509.

### Primary Endpoint: Overall Survival

Source: Reprinted with permission: Van Cutsem E et al. ASCO 2009; Abstract LBA4509.
Secondary Endpoint: Progression-Free Survival

![Graph showing progression-free survival with median times for FC + T and FC treatments.]

<table>
<thead>
<tr>
<th>Events</th>
<th>PFS (months)</th>
<th>HR</th>
<th>95% CI</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC + T</td>
<td>226</td>
<td>6.7</td>
<td>0.71</td>
<td>0.59, 0.85</td>
</tr>
<tr>
<td>FC</td>
<td>235</td>
<td>5.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Source: Reprinted with permission: Van Cutsem E et al. ASCO 2009; Abstract LBA4509.

Secondary Endpoint: Tumor Response Rate

![Graph showing tumor response rates with intent-to-treat comparison for F+C + trastuzumab and F+C.]

- **CR (Complete Response)**: F+C + trastuzumab 2.4%, F+C 5.4%, p=0.0599
- **PR (Partial Response)**: F+C + trastuzumab 32.1%, F+C 41.8%, p=0.0145
- **ORR (Overall Response Rate)**: F+C + trastuzumab 34.5%, F+C 47.3%, p=0.0017

Source: Reprinted with permission: Van Cutsem E et al. ASCO 2009; Abstract LBA4509.
**Safety: Cardiac AEs**

<table>
<thead>
<tr>
<th></th>
<th>FC</th>
<th></th>
<th>FC + T</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
<td>All</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Total cardiac AEs</td>
<td>6%</td>
<td>3%</td>
<td>6%</td>
<td>1%</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Asymptomatic LVEF decline</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>1.1%</td>
<td>1.1%</td>
<td>5.9%</td>
<td>4.6%</td>
</tr>
<tr>
<td>&lt;50% and by ≥ 10%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiac AEs leading to death</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>Cardiac AEs related to treatment</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
<td>&lt;1%</td>
</tr>
</tbody>
</table>

Source: Van Cutsem E et al. ASCO 2009; Abstract LBA4509.

**Summary and Conclusions**

- ToGA met its primary OS endpoint
  - Trastuzumab reduced the risk of death by 26% when combined with fluoropyrimidine/cisplatin (HR=0.74)
  - Trastuzumab prolongs median survival by nearly 3 months (11.1 vs 13.8 months; p = 0.0046) in patients with HER2-positive advanced GC
- All secondary efficacy endpoints (PFS, TTP, ORR, CBR, DoR) significantly improved with the addition of trastuzumab
- Addition of trastuzumab to chemotherapy was well tolerated, with no difference in the overall safety profile between treatment arms, including cardiac AEs
- Trastuzumab in combination with chemotherapy is a new treatment option for patients with HER2-positive advanced GC

Source: Van Cutsem E et al. ASCO 2009; Abstract LBA4509.
Pathological Features of Advanced Gastric Cancer (GC): Relationship to Human Epidermal Growth Factor Receptor 2 (HER2) Positivity in the Global Screening Programme of the ToGA Trial

Bang Y et al.
ASCO 2009; Abstract 4556. (Poster)

Introduction

- HER2 positivity rates in GC range from 6-35%, with variability possibly due to small sample sizes in studies, testing methods and/or scoring criteria used

- Prior to ToGA, a validation study assessed protocols for IHC and FISH in advanced GC
  - A modified version of the HercepTest™ (Dako) scoring system was agreed upon by a panel of international pathology experts

- **Current study objective**: Report results of the ToGA trial screening program, including HER2 status in patients with advanced GC who were screened using the validated HER2 testing protocol

Source: Bang Y et al. ASCO 2009; Abstract 4556.
HER2 Testing and Interpretation

- GC samples were analyzed at a central laboratory using both IHC and FISH to determine HER2 status, as recommended by the validation study for HER2 testing in GC
  - IHC HER2 scoring used the following modified HercepTest parameters: staining intensity; complete/incomplete membrane staining; percentage of stained cells; incomplete membrane staining due to lumen/other reason
  - For FISH, HER2 positivity defined as a HER2:CEP17 ratio of $\geq 2$

- HER2 positivity defined as IHC 3+ or FISH-positive

Source: Bang Y et al. ASCO 2009; Abstract 4556.

Modified HercepTest HER2 Scoring System for GC

<table>
<thead>
<tr>
<th>Staining characteristics</th>
<th>Score/classification</th>
</tr>
</thead>
<tbody>
<tr>
<td>No staining or membrane staining in $&lt;10%$ of cells</td>
<td>0/negative</td>
</tr>
<tr>
<td>Faint/barely perceptible membrane staining in $&gt;10%$ of cells; cells are only stained in part of their membrane</td>
<td>1+/negative</td>
</tr>
<tr>
<td>Weak to moderate complete or basolateral membrane staining in $&gt;10%$ of tumor cells</td>
<td>2+/equivocal</td>
</tr>
<tr>
<td>Moderate to strong complete or basolateral membrane staining in $&gt;10%$ of tumor cells</td>
<td>3+/positive</td>
</tr>
<tr>
<td>Biopsy (not surgery) samples with cohesive IHC 3+ and/or FISH+ clones are considered positive irrespective of size, i.e. $&lt;10%$ of tumor cells</td>
<td></td>
</tr>
</tbody>
</table>

Source: Bang Y et al. ASCO 2009; Abstract 4556.
HER2 Positivity Screening Results

- 3,807 tumor samples from 24 countries assessed for HER2 status in a central laboratory using the modified scoring system
  - 3,667 samples evaluable
  - 810 defined as HER2 positive, for a HER2 positivity rate of 22.1%
- HER2 positivity varied by:
  - Tumor site: GEJ cancer vs stomach cancer (33.2% vs 20.9%, \( p < 0.001 \))
  - Histologic subtype: Intestinal vs diffuse/mixed (32.2% vs 6.1%/20.4%, \( p < 0.001 \))
  - Sample preparation: Biopsy vs surgery (23.1% vs 19.9%, \( p = 0.03 \))
    - Biopsy samples more likely to be HER2-positive than surgery samples when analyzed by FISH (\( p = 0.01 \)) rather than by IHC (\( p = 0.59 \))
- Concordance rate between IHC and FISH with modified HER2 scoring system: 87.2% (N= 3,280)

Source: Bang Y et al. ASCO 2009; Abstract 4556.

Summary and Conclusions

- The ToGA screening program detected a HER2 positivity rate of 22.1% in advanced GC, which is comparable to rates observed in breast cancer
- Gastric tumors are more heterogeneous and complex than breast cancer. Therefore, breast cancer HER2 scoring and evaluation cannot be directly applied to GC
- Both IHC and ISH should be used to determine HER2 status, with IHC as the primary testing modality followed by ISH
- Comparison of these screening data against ToGA efficacy data will enable the clinical significance of the modified HER2 testing scoring system to be assessed

Source: Bang Y et al. ASCO 2009; Abstract 4556.
ToGA ASCO Discussion: Trastuzumab in Gastro-oesophageal Cancer – Future Directions (Cunningham)

- Efficacy of trastuzumab monotherapy
- Maintenance monotherapy after triplet regimens
- Continuation beyond progression in association with second-line therapy as in breast cancer (Von Minckwitz et al, JCO 2009)
- Role of trastuzumab in the peri-operative setting
- Other potential biomarkers to further select patients (currently under evaluation in breast cancer)

Ongoing Randomised Phase III Studies of Targeted Agents in Gastric Cancer

<table>
<thead>
<tr>
<th>Trial Name</th>
<th>Treatment Regimen</th>
<th>Accrual Goal</th>
<th>Trial Status</th>
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<tbody>
<tr>
<td>AVAGAST</td>
<td>Capecitabine, cisplatin +/- bevacizumab</td>
<td>760</td>
<td>Closed</td>
</tr>
<tr>
<td>EXPAND</td>
<td>Cisplatin, capecitabine +/- cetuximab</td>
<td>870</td>
<td>Open</td>
</tr>
<tr>
<td>REAL3</td>
<td>Epirubicin, oxaliplatin, capecitabine +/- panitumumab</td>
<td>730</td>
<td>Open</td>
</tr>
<tr>
<td></td>
<td><strong>Patients selected for HER2 over-expression</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LoGIC</td>
<td>Capecitabine, oxaliplatin +/- lapatinib</td>
<td>410</td>
<td>Open</td>
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<tr>
<td></td>
<td><strong>Peri-operative setting</strong></td>
<td></td>
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</tr>
<tr>
<td>MRC-STO3</td>
<td>Epirubicin, cisplatin, capecitabine +/- bevacizumab</td>
<td>1100</td>
<td>Open</td>
</tr>
</tbody>
</table>
**DR BLANKE:** The concept tested in ToGA is actually not new — it’s been floating around for at least 15 years, but the Belgian group actually pulled it off.

**DR LOVE:** I thought HER2-positive gastric cancer was very uncommon but according to this study, it accounted for 22 percent of tumors — like breast cancer.

**DR BLANKE:** That’s exactly right and that’s what killed the trial proposals in the past — people did not predict that high a number. There is one caveat, namely that there was differential expression of HER2 depending on the pathologic type of gastric cancer, and at ASCO the question was raised as to whether the proportions of diffuse and intestinal gastric cancer were different in North America, and that the percent of HER2-positive tumors might be quite a bit lower. I don’t think we know the answer to that very important critique. The patients in the ToGA trial were from 24 countries in Asia, Australia, Europe, Latin America and South Africa, but no North American centers.

**DR LOVE:** What’s the bottom line on what they found?

**DR BLANKE:** They compared chemotherapy with or without trastuzumab as first-line treatment of metastatic disease with the primary study endpoint of overall survival, and there was a statistically and clinically meaningful improvement in overall survival. Everything else went along with that in terms of tumor response rate and progression-free survival, and they didn’t find any major toxicity issues, including cardiac problems. So they now feel that this is an option for HER2-positive gastric cancer.

**DR LOVE:** What’s your take on that conclusion?

**DR BLANKE:** Our GI tumor group met yesterday to talk about this possibility. It’s a little bit more complicated in Canada, as you can imagine. But I can tell you that if I were back in the US and if I could get the trastuzumab paid for, I’d be using it. From a research perspective the really big area that needs to be tested now is the adjuvant setting — just like with breast cancer — with the hope that this could have a huge impact on a relatively small population.

*Dr Blanke is Systemic Therapy Provincial Program Leader at the BC Cancer Agency as well as the Head of the Division of Medical Oncology at the University of British Columbia in Vancouver, British Columbia, Canada.*