The management of advanced gastric cancer: towards individualized therapy

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Digestive Oncology
Leuven, Belgium
**Advanced Gastric Cancer**

In patients with adequate PS, combination chemotherapy can improve survival and QoL


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**Phase III trials evaluating addition of biologicals in gastric and GEJ cancer**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Regimen</th>
<th>No.pts</th>
<th>Status</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA*</td>
<td>5-FU/Cape + cisplatin +/- trastuzumab</td>
<td>584</td>
<td>Reported¹</td>
</tr>
<tr>
<td>LoGIC*</td>
<td>Cape + oxali. +/- lapatinib</td>
<td>410</td>
<td>Ongoing</td>
</tr>
<tr>
<td>AVAGAST</td>
<td>Cape + cisplatin +/- bevacizumab</td>
<td>760</td>
<td>Reported²</td>
</tr>
<tr>
<td>EXPAND</td>
<td>Cape + cisplatin +/- cetuximab</td>
<td>870</td>
<td>Recruited</td>
</tr>
<tr>
<td>REAL-3</td>
<td>EOX +/- panitumumab</td>
<td>730</td>
<td>Ongoing</td>
</tr>
<tr>
<td>GRANITE**</td>
<td>BSC +/- everolimus</td>
<td>600</td>
<td>Recruited</td>
</tr>
</tbody>
</table>

¹Bang Y, Van Cutsem E et al. ASCO 2009
²Kang Y, Van Cutsem E, ASCO 2010

* HER2+ patients only: ** 2ª / 3ª line
Trastuzumab

- Inhibits HER2-mediated signalling in HER2-positive tumors
- Prevents HER2 activation by blocking extracellular domain cleavage
- Activates antibody-dependent cellular cytotoxicity

Some gastric adenocarcinomas are HER2 positive

- Trastuzumab is effective against HER2-overexpressing GC cell lines *in vitro* and *in vivo*

Differences in HER2 testing between breast and gastric cancers

- Pre-ToGA international validation study investigated HER2 testing of 168 gastric cancer samples: concordance in 93% of samples
- Histological differences between gastric and breast cancers necessitate minor modifications to the HER2-scoring system for gastric cancer

- Tumour heterogeneity is more common in gastric cancer
- Incomplete membrane staining with IHC is more common in gastric cancer

Hofmann M et al Histopathology 2008
<table>
<thead>
<tr>
<th>Score</th>
<th>Surgical Specimen Staining Pattern</th>
<th>Biopsy Specimen Staining Pattern</th>
<th>HER2 Overexpr. Assessment</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No reactivity or membranous reactivity in &lt; 10% of tumor cells</td>
<td>No reactivity or no membranous reactivity in any tumor cell</td>
<td>Negative</td>
</tr>
<tr>
<td>1+</td>
<td>Faint or barely perceptible membranous reactivity in ≥ 10% of tumor cells; cells are reactive only in part of their membrane</td>
<td>Tumor cell cluster with faint or barely perceptible membranous reactivity irrespective of % of tumor cells stained</td>
<td>Negative</td>
</tr>
<tr>
<td>2+</td>
<td>Weak to moderate complete, basolateral or lateral membranous reactivity in ≥ 10% of tumor cells</td>
<td>Tumor cell cluster with weak to moderate complete, basolateral or lateral membranous reactivity irrespective of % of tumor cells stained</td>
<td>Equivocal</td>
</tr>
<tr>
<td>3+</td>
<td>Strong complete, basolateral or lateral membranous reactivity in ≥ 10% of tumor cells</td>
<td>Tumor cell cluster with strong complete, basolateral or lateral membranous reactivity irrespective of % of tumor cells stained</td>
<td>Positive</td>
</tr>
</tbody>
</table>

Bang Y, Van Cutsem E et al. Lancet 2010

**HER2 positivity in subgroups**

3807 screened gastric adenocarcinoma

- **HER2 positive:** 22% (IHC 3+ and/or FISH +)
- **Histologic subtype** (Lauren classification):
  - Intestinal type: 32.2 % (n= 1884)
  - Diffuse type: 6.1 % (n= 1098)
  - Mixed type: 20.4 % (n= 637)
- **Tumor site**
  - GEJ: 33.2 %
  - Gastric: 20.9 %
- **Endoscopic biopsies = surgical biopsies**
- **Asia = Europe**

Bang Y, Van Cutsem E. ASCO 2009
ToGA trial design
Phase III, randomized, open-label, international, multicenter study

3807 patients screened
810 HER2-positive (22.1%)

HER2-positive advanced GC (n=584)

- HER2-positive tumour (centrally assessed)
  - IHC 3+ and/or FISH+
- Stratification factors
  - advanced vs metastatic
  - GC vs GEJ
  - measurable vs non-measurable
  - ECOG PS 0-1 vs 2
  - capecitabine vs 5-FU

5-FU or capecitabine + cisplatin (n=290)
5-FU or capecitabine + cisplatin + trastuzumab (n=294)

*Chosen at investigator’s discretion
GEJ, gastroesophageal junction

Van Cutsem E et al; LBAbstract 4509, ASCO 2009
Bang Y, Van Cutsem E et al Lancet 2010

Primary end point: OS

<table>
<thead>
<tr>
<th>Event</th>
<th>FC + T</th>
<th>FC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. at risk</td>
<td>294</td>
<td>290</td>
</tr>
<tr>
<td>Median</td>
<td>13.8</td>
<td>11.1</td>
</tr>
<tr>
<td>Median OS</td>
<td>11.1</td>
<td>13.8</td>
</tr>
<tr>
<td>HR</td>
<td>0.74</td>
<td>0.60, 0.91</td>
</tr>
<tr>
<td>95% CI</td>
<td>0.0046</td>
<td></td>
</tr>
</tbody>
</table>

Van Cutsem E et al; LBAbstract 4509, ASCO 2009
Bang Y, Van Cutsem E et al Lancet 2010
### Efficacy end points

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>F+C n=290</th>
<th>F+C + trastuzumab n=294</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>OS, median months</td>
<td>11.1</td>
<td>13.8</td>
<td>0.74 (0.60, 0.91)</td>
<td>0.0046</td>
</tr>
<tr>
<td>PFS, median months</td>
<td>5.5</td>
<td>6.7</td>
<td>0.71 (0.59, 0.85)</td>
<td>0.0002</td>
</tr>
<tr>
<td>TTP, median months</td>
<td>5.6</td>
<td>7.1</td>
<td>0.70 (0.58, 0.85)</td>
<td>0.0003</td>
</tr>
<tr>
<td>ORR, %</td>
<td>34.5</td>
<td>47.3</td>
<td>1.70* (1.22, 2.38)</td>
<td>0.0017</td>
</tr>
<tr>
<td>Patients with measurable disease</td>
<td>37.4</td>
<td>50.9</td>
<td>1.74* (1.23, 2.46)</td>
<td>0.0017</td>
</tr>
<tr>
<td>DoR, median months</td>
<td>4.8</td>
<td>6.9</td>
<td>0.54 (0.40, 0.73)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Clinical benefit rate, %</td>
<td>69.3</td>
<td>78.9</td>
<td>1.66 (1.14, 2.41)</td>
<td>0.0081</td>
</tr>
</tbody>
</table>

* Odds ratio

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### OS in IHC2+/FISH+ or IHC3+ (exploratory analysis)

<table>
<thead>
<tr>
<th>Event</th>
<th>Median OS</th>
<th>HR 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC + T</td>
<td>120</td>
<td>16.0</td>
</tr>
<tr>
<td>FC</td>
<td>136</td>
<td>11.8</td>
</tr>
</tbody>
</table>

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* Odds ratio

Van Cutsem E et al; ECCO/ESMO 2009
Bang Y, Van Cutsem E et al Lancet 2010

Van Cutsem E et al; LBAbstract 4509, ASCO 2009
Bang Y, Van Cutsem E et al Lancet 2010
Safety: cardiac AEs

<table>
<thead>
<tr>
<th>Cardiac event, n (%)</th>
<th>F+C n=290</th>
<th>F+C + trastuzumab n=294</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>All</td>
<td>Grade 3/4</td>
</tr>
<tr>
<td>Cardiac AEs, total</td>
<td>18 (6)</td>
<td>9 (3)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>2 (&lt;1)</td>
<td>2 (&lt;1)</td>
</tr>
<tr>
<td>LVEF drops*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;50%</td>
<td>2 (1.1)</td>
<td></td>
</tr>
<tr>
<td>&lt;50% and by ≥10%</td>
<td>2 (1.1)</td>
<td></td>
</tr>
<tr>
<td>Cardiac AEs leading to death</td>
<td>2 (&lt;1)</td>
<td>Cardiac arrest; cardio-respiratory arrest</td>
</tr>
</tbody>
</table>

*Measured at baseline and every 12 weeks; MI, myocardial infarction

Van Cutsem E et al; LBAbstract 4509, ASCO 2009
Bang Y, Van Cutsem E et al Lancet 2010

Suggested HER2 testing algorithm in GC/GEJ cancer

Patient tumour sample

IHC

0 +1 +2 retest +3

FISH/SISH*

- + Eligible for trastuzumab

*cut off for FISH, SISH = HER2:CEP17 ratio ≥2

Van Cutsem E et al; ECCO/ESMO 2009
Bang Y, Van Cutsem E et al Lancet 2010
Breakdown of successful HER2 IHC and FISH screening

<table>
<thead>
<tr>
<th></th>
<th>IHC 0,</th>
<th>IHC 1+,</th>
<th>IHC 2+,</th>
<th>IHC 3+,</th>
<th>Total,</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>FISH+</td>
<td>94 (4.9)</td>
<td>96 (15.7)</td>
<td>212 (54.6)</td>
<td>354 (94.9)</td>
<td>756 (23.0)</td>
</tr>
<tr>
<td>FISH-</td>
<td>1815 (95.1)</td>
<td>514 (84.3)</td>
<td>176 (45.4)</td>
<td>19 (5.1)</td>
<td>2524 (77.0)</td>
</tr>
<tr>
<td>Total</td>
<td>1909 (100)</td>
<td>610 (100)</td>
<td>388 (100)</td>
<td>373 (100)</td>
<td>3280 (100.0)</td>
</tr>
</tbody>
</table>

Concordance rate between FISH and IHC: 87.2%

Bang Y, Van Cutsem E et al. ASCO 2009

Median OS increased to >1 year with Trastuzumab-based treatment

LOGiC: Phase III Trial of Lapatinib + CapeOx in HER2+ Gastric Cancer

Patients with HER2-amplified locally advanced, unresectable, or metastatic gastric, esophageal, or GEJ cancer

(Planned N = 535)

- Primary endpoint: OS (was PFS)
- Data expected mid-2012

ClinicalTrials.gov. NCT00680901.

Pertuzumab & Trastuzumab Bind Distinct Epitopes on HER2 Extracellular Domain

- Activates ADCC
- Prevents HER2 domain cleavage
- Inhibits HER2-mediated signaling pathways

### EGFR Family Inhibitors in Gastric Cancer

**Phase III studies**

<table>
<thead>
<tr>
<th>Target</th>
<th>Study</th>
<th>Control arm</th>
<th>Experimental arm</th>
</tr>
</thead>
<tbody>
<tr>
<td>EGFR</td>
<td>REAL-3&lt;sup&gt;1&lt;/sup&gt;</td>
<td>EOX</td>
<td>EOX + Panitumumab</td>
</tr>
<tr>
<td>EGFR</td>
<td>MATRIX&lt;sup&gt;2&lt;/sup&gt;</td>
<td>ECX</td>
<td>ECX + Matuzumab</td>
</tr>
<tr>
<td>EGFR</td>
<td>EXPAND&lt;sup&gt;3&lt;/sup&gt;</td>
<td>XP</td>
<td>XP + Cetuximab</td>
</tr>
<tr>
<td>EGFR/HER2</td>
<td>LOGIC&lt;sup&gt;4&lt;/sup&gt;</td>
<td>CapeOx</td>
<td>CapeOx + Lapatinib</td>
</tr>
<tr>
<td>EGFR/HER2</td>
<td>EGF104578 - 2&lt;sup&gt;nd&lt;/sup&gt; line&lt;sup&gt;5&lt;/sup&gt;</td>
<td>Paclitaxel</td>
<td>Paclitaxel + Lapatinib</td>
</tr>
<tr>
<td>HER2</td>
<td>TOGA&lt;sup&gt;6&lt;/sup&gt;</td>
<td>XP/FP</td>
<td>XP/FP + Trastuzumab&lt;sup&gt;6&lt;/sup&gt;</td>
</tr>
</tbody>
</table>


### Conclusions

- Trastuzumab is the first biological to show a survival benefit in gastric cancer
- Trastuzumab in combination with chemotherapy is a new standard option for patients with HER2-positive gastric adenocarcinoma
- Other biologicals under investigation
Save the Date!

22–25 June 2011

Gastrointestinal Cancer

22–25 June 2011
Barcelona, Spain