Biological Targeted Agents in Gastric Cancer

Florian Lordick, MD, PhD

Professor of Oncology
Director of the University Cancer Center UCCL
Leipzig, Germany
Genomic DNA were extracted from flash-frozen tissues or cell pellets using a Qiagen genomic DNA extraction kit (Qiagen, Hilden, Germany), and profiled on Affymetrix SNP 6.0 arrays (Affymetrix, Santa Clara, California, USA).

Gastric Cancer Biology

Gastric Cancer Biology

C

D

Overall survival rate

Overall survival rate

Overall survival rate

Overall survival rate

Number at risk

Number at risk

Number at risk

FGFR2 Low Exp

FGFR2 High Exp

FGFR2 Low Exp

FGFR2 High Exp

p=0.01

p=0.01

p=0.01

p=0.01

n=324

n=72

Deng et al. *Gut* 2012; 61: 673-684
Gastric Cancer Biology

Targeted Therapy

„Personalized Treatment“

Select the right treatment for every individual patient
Biological Treatment Selection

Premisses & Hurdles

- Do we know the relevant target structures?
- Is the detection of these structures reliable?
- Is a targeted treatment/drug available?
- Is the response to this specific treatment predictable?
- Is the targeted treatment feasible and tolerable?
Is the Target Expressed and is it Relevant? Epidermal Growth Factor Receptor Signalling

EGFR family

EGFR: Epidermal Growth Factor Receptor

HER-1 (EGFR)
HER-2
HER-3
HER-4

Reliable Detection of a Target? e.g. HER2 Immunohistochemistry (IHC)

Her2: 2+

With courtesy of Prof. Donhuijsen, Pathologie Braunschweig
Reliable Detection of a Target? e.g. HER2 in situ hybridization (ISH)

With courtesy of Prof. Donhuijsen, Pathologie Braunschweig
Is a targeted treatment available? HER-antibodies and HER-kinase-inhibitors

Inhibition of cancer-cell proliferation and invasion, metastasis, and tumor-induced neoangiogenesis

Induction of cancer-cell cycle arrest and potentiation of antitumor activity of cytotoxic drugs and radiotherapy

Trastuzumab (Herceptin®) in Her2+ Gastric Cancer: ToGA Study

Primary endpoint: survival (superiority)

N=584

Stomach and AEG

Stage IV

Trastuzumab + Cisplatin/FU or Capecitabin q3w
6 cycles; Trastuzumab until progression

Cisplatin/FU or Capecitabine q3w
6 cycles

Bang Y et al. Lancet 2010; 376: 687-697
## ToGA Response Data

<table>
<thead>
<tr>
<th>Response Category</th>
<th>Trastuzumab plus chemotherapy (n=294)</th>
<th>Chemotherapy alone (n=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall tumour response rate</td>
<td>139 (47%)</td>
<td>100 (35%)</td>
</tr>
<tr>
<td>Complete response</td>
<td>16 (5%)</td>
<td>7 (2%)</td>
</tr>
<tr>
<td>Partial response</td>
<td>123 (42%)</td>
<td>93 (32%)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>93 (32%)</td>
<td>101 (35%)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>35 (12%)</td>
<td>53 (18%)</td>
</tr>
<tr>
<td>Missing</td>
<td>27 (9%)</td>
<td>36 (12%)</td>
</tr>
</tbody>
</table>

Bang Y et al. Lancet 2010; 376: 687-697
ToGA Survival

<table>
<thead>
<tr>
<th>Events</th>
<th>Median overall survival (months)</th>
<th>HR (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trastuzumab plus chemotherapy</td>
<td>167</td>
<td>13.8</td>
<td>0.74 (0.60–0.91)</td>
</tr>
<tr>
<td>Chemotherapy alone</td>
<td>182</td>
<td>11.1</td>
<td></td>
</tr>
</tbody>
</table>

Number at risk

<table>
<thead>
<tr>
<th>Trastuzumab plus chemotherapy</th>
<th>294</th>
<th>277</th>
<th>246</th>
<th>209</th>
<th>173</th>
<th>147</th>
<th>113</th>
<th>90</th>
<th>71</th>
<th>56</th>
<th>43</th>
<th>30</th>
<th>21</th>
<th>13</th>
<th>12</th>
<th>6</th>
<th>4</th>
<th>1</th>
<th>0</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemotherapy alone</td>
<td>290</td>
<td>266</td>
<td>223</td>
<td>185</td>
<td>143</td>
<td>117</td>
<td>90</td>
<td>64</td>
<td>47</td>
<td>32</td>
<td>24</td>
<td>16</td>
<td>14</td>
<td>7</td>
<td>6</td>
<td>5</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Bang Y et al. Lancet 2010; 376: 687-697
ToGA: Survival
Her2 Status: IHC 3+ or IHC 2+/FISH+

Bang Y et al. Lancet 2010; 376: 687-697
1st-line Treatment Algorithm 2013
Advanced Stomach Cancer

Immunohistochemie Her2

IHC Score 0/1 → FISH-Test Her2 → FISH - → Platin-Fluoropyrimidin-(Docetaxel)

IHC Score 2

FISH-Test Her2 → FISH + → Trastuzumab + Cisplatin-Fluoropyrimidin

IHC Score 3
HER2 Quality Assurance and Problems

Focal staining in 33% of gastric cancers!

With courtesy of Professor Rüschoff
Heterogeneity and Sampling Errors

2230 Core biopsies from TMA’s of 454 resection specimens
Heterogeneity and Sampling Errors

2230 Core biopsies from TMA's of 454 resection specimens
Heterogeneity and Sampling Errors

2230 Core biopsies from TMA‘s of 454 resection specimen

Core biopsies (from TMA‘s) were compared with whole tissue sections by two independent investigators

HER-2 from whole tissue sections: 8.1 und 8.4% positivity
HER-2 from core biopsies: 6.3 und 6.3% positivity

False negative rate of core biopsies: 24%
False positive rate of core biopsies: 3%
Heterogeneity and Sampling Errors

Practical consequence

When selecting patients for anti-HER2 treatment,…

- Don’t rely on one negative endoscopic biopsy (false-negative rate: 24%)

- Investigate whole tissue sections from resection specimens in addition to endoscopic biopsies (if available)

- Take new biopsies from metastatic sites (if feasible)
FISH, CISH, BDISH or IHC

Rüschoff et al., 2010

Warneke VS... Röcken C. Ann Oncol 2013 Mar;24(3):725-33
Overall concordance between FISH and IHC results was 90.9% (95% CI: 89.2%, 92.5%).
HER2 Results from ToGA

<table>
<thead>
<tr>
<th></th>
<th>Trastuzumab plus chemotherapy (n=294)</th>
<th>Chemotherapy alone (n=290)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FISH positive/IHC 0</td>
<td>23 (8%)</td>
<td>38 (13%)</td>
</tr>
<tr>
<td>FISH positive/IHC 1+</td>
<td>38 (13%)</td>
<td>32 (11%)</td>
</tr>
<tr>
<td>FISH positive/IHC 2+</td>
<td>80 (27%)</td>
<td>79 (27%)</td>
</tr>
<tr>
<td>FISH positive/IHC 3+</td>
<td>131 (45%)</td>
<td>125 (43%)</td>
</tr>
<tr>
<td>FISH negative/IHC 3+</td>
<td>9 (3%)</td>
<td>6 (2%)</td>
</tr>
<tr>
<td>FISH positive/IHC no result</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>FISH no result/IHC 3+</td>
<td>8 (3%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

## HER2 Results from ToGA

<table>
<thead>
<tr>
<th></th>
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<td>6 (2%)</td>
</tr>
<tr>
<td>FISH positive/IHC no result</td>
<td>5 (2%)</td>
<td>2 (1%)</td>
</tr>
<tr>
<td>FISH no result/IHC 3+</td>
<td>8 (3%)</td>
<td>8 (3%)</td>
</tr>
</tbody>
</table>

# HER2 Results from ToGA

### Table A

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Number of patients</th>
<th>Median overall survival (months)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td></td>
<td>584</td>
<td>13.8 vs 11.1</td>
<td>0.74 (0.60-0.91)</td>
</tr>
<tr>
<td>Pre-planned exploratory analysis*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 0/FISH positive</td>
<td></td>
<td>61</td>
<td>10.6 vs 7.2</td>
<td>0.92 (0.48-1.76)</td>
</tr>
<tr>
<td>IHC 1+/FISH positive</td>
<td></td>
<td>70</td>
<td>8.7 vs 10.2</td>
<td>1.24 (0.70-2.20)</td>
</tr>
<tr>
<td>IHC 2+/FISH positive</td>
<td></td>
<td>159</td>
<td>12.3 vs 10.8</td>
<td>0.75 (0.51-1.11)</td>
</tr>
<tr>
<td>IHC 3+/FISH positive</td>
<td></td>
<td>256</td>
<td>17.9 vs 12.3</td>
<td>0.58 (0.41-0.81)</td>
</tr>
<tr>
<td>IHC 3+/FISH negative</td>
<td></td>
<td>15</td>
<td>17.5 vs 17.7</td>
<td>0.83 (0.20-3.38)</td>
</tr>
<tr>
<td>Post-hoc exploratory analysis†</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IHC 0 or 1+/FISH positive</td>
<td></td>
<td>131</td>
<td>10.0 vs 8.7</td>
<td>1.07 (0.70-1.62)</td>
</tr>
<tr>
<td>IHC 2+/FISH positive or IHC 3+</td>
<td></td>
<td>446</td>
<td>16.0 vs 11.8</td>
<td>0.65 (0.51-0.83)</td>
</tr>
</tbody>
</table>

*Favour trastuzumab plus chemotherapy
†Favors chemotherapy alone

European Consensus Conference for external quality assessment in molecular pathology

J. H. van Krieken¹, A. G. Siebers¹ & N. Normanno²* On behalf of the Quality Assurance for Molecular Pathology group†

¹Department of Pathology 824, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands; ²Cell Biology and Biotherapy Unit, INT-Fondazione Pascale, Naples, Italy

Received 7 December 2012; revised 14 March 2013; accepted 15 March 2013

Molecular testing of tumor samples to guide treatment decisions is of increasing importance. Several drugs have been approved for treatment of molecularly defined subgroups of patients, and the number of agents requiring companion diagnostics for their prescription is expected to rapidly increase. The results of such testing directly influence the management of individual patients, with both false-negative and false-positive results being harmful for patients. In this
EGFR-Family-Dimers

### Table 3. HER Dimerization Observed in Gastric Carcinomas

<table>
<thead>
<tr>
<th>Pair</th>
<th>Patient Cases</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER1/HER3</td>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>HER1/HER4</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>HER2/HER3</td>
<td>28</td>
<td>15</td>
</tr>
<tr>
<td>HER2/HER4</td>
<td>10</td>
<td>5.5</td>
</tr>
<tr>
<td>HER3/HER4</td>
<td>51</td>
<td>28</td>
</tr>
</tbody>
</table>

Abbreviation: HER, human epidermal growth factor receptor.
Anti-HER2/HER3-directed Therapy

Trastuzumab-Pertuzumab-Combination (Breast Cancer)

n=808 pts
HER-2 pos., metastatic BC
- docetaxel + trastuzumab +/- pertuzumumab

Pertuzumab plus Trastuzumab plus Docetaxel for Metastatic Breast Cancer

José Baselga, M.D., Ph.D., Javier Cortés, M.D., Sung-Bae Kim, M.D., Seock-Ah Im, M.D., Roberto Hegg, M.D., Young-Hyuck Im, M.D., Laslo Roman, M.D., José Luiz Pedrini, M.D., Tadeusz Pienkowski, M.D., Adam Krott, Ph.D., Emma Clark, M.Sc., Mark C. Benyunes, M.D., Graham Ross, F.F.P.M., and Sandra M. Swain, M.D., for the CLEOPATRA Study Group
Trastuzumab-Pertuzumab-Combination (Stomach Cancer)

Ongoing: JACOB Study (RCT Stage IV)

Ongoing: INNOVATION Study (RCT Stage IV)
Trastuzumab-DM1

Inhibition of microtubule polymerization

Emtansine release

Lysosome

Internalization

From Spector NL, Blackwell KL. J Clin Oncol 2009
Trastuzumab Emtansine for HER2-Positive Advanced Breast Cancer

Sunil Verma, M.D., David Miles, M.D., Luca Gianni, M.D., Ian E. Krop, M.D., Ph.D., Manfred Welslau, M.D., José Baselga, M.D., Ph.D., Mark Pegram, M.D., Do-Youhn Oh, M.D., Ph.D., Véronique Diéras, M.D., Ellie Guardino, M.D., Ph.D., Liang Fang, Ph.D., Michael W. Lu, Pharm.D., Steven Olsen, M.D., Ph.D., and Kim Blackwell, M.D., for the EMILIA Study Group

BACKGROUND
Trastuzumab emtansine (T-DM1) is an antibody–drug conjugate incorporating the human epidermal growth factor receptor 2 (HER2)–targeted antitumor properties of trastuzumab with the cytotoxic activity of the microtubule inhibitory agent DM1. The
Trastuzumab-DM1 (Breast Cancer)

2nd Interims Survival Analysis

- Median No. of Months: 25.1, 30.9
- No. of Events: 182, 149
- Stratified hazard ratio: 0.68 (95% CI, 0.55–0.85), P<0.001
- Efficacy stopping boundary, P=0.0037 or hazard ratio, 0.73

Overall Survival (%)

No. at Risk
Lapatinib–capecitabine
496 471 453 435 403 368 297 240 204 159 133 110 86 63 45 27 17 7 4
T-DM1
495 485 474 457 439 418 349 293 242 197 164 136 111 86 62 38 28 13 5
# Trastuzumab-DM1 (Breast Cancer)

## Table 3. Adverse Events in the Safety Population.*

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Lapatinib plus Capecitabine (N = 488)</th>
<th>T-DM1 (N = 490)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events of Any Grade</td>
<td>Grade 3 or 4 Events</td>
</tr>
<tr>
<td>Any event</td>
<td>477 (97.7)</td>
<td>278 (57.0)</td>
</tr>
<tr>
<td>Specific events†</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>389 (79.7)</td>
<td>101 (20.7)</td>
</tr>
<tr>
<td>Palmar–plantar erythrodynasthesia</td>
<td>283 (58.0)</td>
<td>80 (16.4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>143 (29.3)</td>
<td>22 (4.5)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>42 (8.6)</td>
<td>21 (4.3)</td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>42 (8.6)</td>
<td>20 (4.1)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>136 (27.9)</td>
<td>17 (3.5)</td>
</tr>
<tr>
<td>Nausea</td>
<td>218 (44.7)</td>
<td>12 (2.5)</td>
</tr>
<tr>
<td>Mucosal inflammation</td>
<td>93 (19.1)</td>
<td>11 (2.3)</td>
</tr>
<tr>
<td>Anemia</td>
<td>39 (8.0)</td>
<td>8 (1.6)</td>
</tr>
<tr>
<td>Elevated ALT</td>
<td>43 (8.8)</td>
<td>7 (1.4)</td>
</tr>
<tr>
<td>Elevated AST</td>
<td>46 (9.4)</td>
<td>4 (0.8)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>12 (2.5)</td>
<td>1 (0.2)</td>
</tr>
</tbody>
</table>
Trastuzumab-DM1 (Stomach Cancer)

Ongoing: GATSBY Study (RCT Stage IV 2nd line)

**Arm A:** trastuzumab emtansine 3.6 mg/kg Q3W IV

**Arm B:** trastuzumab emtansine 2.4 mg/kg QW IV

**Arm C (control arm):** Docetaxel 75 mg/m² Q3W IV or paclitaxel 80 mg/m² QW IV according to investigator choice. The choice of taxane will be selected on an individual patient basis and must be made prior to randomization and remain consistent throughout the study, unless the patient is intolerant due to a hypersensitivity reaction or toxicity (see below for further details).
Lapatinib in combination with capecitabine plus oxaliplatin in HER2-positive advanced or metastatic gastric, esophageal, or gastroesophageal adenocarcinoma: The TRIO-013/LOGiC Trial

JR Hecht, Y Bang, S Qin, H Chung, J Xu, J Park, K Jeziorski, Y Shparyk, PM Hoff, AF Sobrero, P Salman, J Li, S Protsenko, ME Buyse, K Afenjar, T Kaneko, A Kemner, S Santillana, MF Press, DJ Slamon
**Lapatinib**

**R 1:1**

**Arm A:** CapeOX q3w plus daily Lapatinib

**Arm B:** CapeOX q3w plus Placebo

**Study population**
Overexpression or Amplification of HER2 (IHC 2+ plus FISH+ or IHC 3+ or FISH, CISH or SISH amplified)

**Primary endpoint**
Overall Survival (10.3 -> 14 months), n=545

**Sec. Endpoint**
Progression-free Survival, Response, toxicity

**Stratification**
Previous adj. therapy; region Asia, North America, ROW
Lapatinib

- 545 patients recruited in 186 centers (2008-2012)
- 487 patients for the primary efficacy analysis (central: FISH+).
- 87% stomach cancers, 13% GEJ/esophageal cancers
## Lapatinib

<table>
<thead>
<tr>
<th></th>
<th>CapeOx + Lapatinib (N=249)</th>
<th>CapeOx + Placebo (N=238)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Complete response</strong></td>
<td>6 (2%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td><strong>Partial response</strong></td>
<td>126 (51%)</td>
<td>90 (38%)</td>
</tr>
<tr>
<td><strong>Stable Disease</strong></td>
<td>70 (28%)</td>
<td>94 (39%)</td>
</tr>
<tr>
<td><strong>Disease Progression</strong></td>
<td>20 (8%)</td>
<td>22 (9%)</td>
</tr>
<tr>
<td><strong>Not evaluable/unknown</strong></td>
<td>27 (11%)</td>
<td>27 (11%)</td>
</tr>
<tr>
<td><strong>Overall RR</strong></td>
<td>53% (95%CI : 46.6–59.3)</td>
<td>40% (95% CI : 33.6–46.4)</td>
</tr>
<tr>
<td><strong>Median Duration of Response (month)</strong></td>
<td>7.3 (95%CI : 6.4–8.4)</td>
<td>5.6 (95%CI : 4.8–6.0)</td>
</tr>
<tr>
<td><strong>ORR by region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>63 %</td>
<td>56 %</td>
</tr>
<tr>
<td>Asia</td>
<td>65 %</td>
<td>39 %</td>
</tr>
<tr>
<td>ROW</td>
<td>44 %</td>
<td>40 %</td>
</tr>
</tbody>
</table>
Lapatinib

HR for OS 0.91 (p=0.35; median survival 12.2 versus 10.5 months)
Lapatinib

Primary efficacy population (N=487)

Region
- Asia (n=193)
- North America (n=17)
- Rest of World (n=277)

Prior adjuvant use
- Yes (n=38)
- No (n=449)

Age (years)
- <60 (n=236)
- ≥60 (n=251)

Baseline ECOG status
- 0−1 (n=444)
- 2 (n=43)

Primary site
- Esophagus (n=20)
- GE Junction (n=43)
- Gastric (n=424)

Histological type
- Diffuse (n=19)
- Intestinal (n=436)
- Other (n=32)

Pylorus intact
- Yes (n=373)
- No (n=114)

HER2 status (all FISH+)
- IHC 0 (n=27)
- IHC 1+ (n=54)
- IHC 2+ (n=108)
- IHC 3+ (n=297)
- IHC 0−1+ (n=81)
- IHC 2−3+ (n=405)

Hazard ratio (95% CI)

- 0.91 (0.73, 1.12)
- 0.68 (0.48, 0.96)
- 1.61 (0.53, 4.83)
- 1.04 (0.79, 1.37)
- 1.52 (0.68, 3.41)
- 0.83 (0.67, 1.04)
- 0.69 (0.51, 0.94)
- 1.08 (0.81, 1.45)
- 0.88 (0.70, 1.10)
- 0.76 (0.41, 1.44)
- 0.87 (0.32, 2.35)
- 0.90 (0.44, 1.85)
- 0.89 (0.71, 1.11)
- 0.64 (0.25, 1.65)
- 0.93 (0.75, 1.17)
- 0.58 (0.26, 1.29)
- 0.80 (0.63, 1.01)
- 1.06 (0.67, 1.68)
- 0.56 (0.24, 1.31)
- 1.16 (0.61, 2.20)
- 0.79 (0.50, 1.25)
- 0.90 (0.69, 1.18)
- 0.91 (0.55, 1.51)
- 0.86 (0.68, 1.09)

Hazard Ratio (CapeOx+L / CapeOx+P)

Favors CapeOx+L
Favors CapeOx+P
EGFR (HER1) in Gastric Cancer

mixed, 3+

intestinal, 0-3+

diffuse, 2+

diffuse, 1+

Gamboa et al. Mod Pathol 2004;17:579-87
EGFR (HER1) in Gastric Cancer

Cetuximab plus oxaliplatin/leucovorin/5-fluorouracil in first-line metastatic gastric cancer: a phase II study of the Arbeitsgemeinschaft Internistische Onkologie (AIO)

<table>
<thead>
<tr>
<th>FUFOX + Cetuximab</th>
<th>n</th>
<th>Response (%)</th>
<th>mTTP (Mon)</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Lordick F</em>, et al. <em>BJC</em> 2010</td>
<td>46</td>
<td>65% 95% CI, 50–79%</td>
<td>7.6 95% CI, 5.0–10.1</td>
</tr>
</tbody>
</table>

EGFR (HER1) in Gastric Cancer

EGFR gene amplification:
EGFR: 8.20 signals per nucleus
EGFR/CEP7 ratio: 1.36

EGFR (red), chromosome 7 (green)

EGFR FISH ≥4.0
Log-rank P=0.011

EGFR FISH <4.0

Overall survival time (days)
Survival (%)

Luber B,… Lordick F. BMC Cancer 2011;11:509
EGFR (HER1) in Gastric Cancer

Randomized Controlled Trial:

- **Cisplatin**: 80mg/m² d1
- **Capecitabine**: 1000mg/m² twice daily; d1-14 q3w
- **Cetuximab**: 400mg/m² loading dose, then 250mg/m² per week

- Until radiographically documented PD or unacceptable toxicity
- Primary endpoint: Progression Free Survival (PFS) time

EGFR (HER1) in Gastric Cancer

EGFR (HER1) in Gastric Cancer

<table>
<thead>
<tr>
<th>Subgroup by EGFR IHC score</th>
<th>Median PFS (months)</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;150 (n=715)</td>
<td>4.4 vs 5.6</td>
<td>1.17 (0.97–1.41)</td>
</tr>
<tr>
<td>≥150 (n=59)</td>
<td>5.7 vs 4.5</td>
<td>0.67 (0.33–1.36)</td>
</tr>
<tr>
<td>&lt;160 (n=720)</td>
<td>4.4 vs 5.6</td>
<td>1.16 (0.97–1.40)</td>
</tr>
<tr>
<td>≥160 (n=54)</td>
<td>5.5 vs 4.2</td>
<td>0.70 (0.34–1.44)</td>
</tr>
<tr>
<td>&lt;170 (n=728)</td>
<td>4.4 vs 5.6</td>
<td>1.17 (0.97–1.41)</td>
</tr>
<tr>
<td>≥170 (n=46)</td>
<td>5.5 vs 4.2</td>
<td>0.62 (0.28–1.35)</td>
</tr>
<tr>
<td>&lt;180 (n=732)</td>
<td>4.4 vs 5.6</td>
<td>1.17 (0.97–1.41)</td>
</tr>
<tr>
<td>≥180 (n=42)</td>
<td>5.5 vs 4.1</td>
<td>0.62 (0.27–1.42)</td>
</tr>
<tr>
<td>&lt;190 (n=740)</td>
<td>4.4 vs 5.6</td>
<td>1.17 (0.97–1.41)</td>
</tr>
<tr>
<td>≥190 (n=34)</td>
<td>5.5 vs 4.1</td>
<td>0.54 (0.22–1.29)</td>
</tr>
<tr>
<td>&lt;200 (n=745)</td>
<td>4.4 vs 5.6</td>
<td>1.16 (0.96–1.39)</td>
</tr>
<tr>
<td>≥200 (n=29)</td>
<td>6.0 vs 4.2</td>
<td>0.52 (0.20–1.34)</td>
</tr>
<tr>
<td>&lt;210 (n=749)</td>
<td>4.4 vs 5.6</td>
<td>1.16 (0.96–1.39)</td>
</tr>
<tr>
<td>≥210 (n=25)</td>
<td>7.5 vs 4.3</td>
<td>0.41 (0.13–1.26)</td>
</tr>
<tr>
<td>&lt;220 (n=754)</td>
<td>4.4 vs 5.6</td>
<td>1.16 (0.97–1.40)</td>
</tr>
<tr>
<td>≥220 (n=20)</td>
<td>7.5 vs 4.1</td>
<td>0.29 (0.09–0.96)</td>
</tr>
<tr>
<td>&lt;230 (n=756)</td>
<td>4.4 vs 5.6</td>
<td>1.16 (0.97–1.39)</td>
</tr>
<tr>
<td>≥230 (n=18)</td>
<td>7.5 vs 4.1</td>
<td>0.31 (0.09–1.03)</td>
</tr>
</tbody>
</table>

EGFR (HER1) in Gastric Cancer

Epirubicin, oxaliplatin, and capecitabine with or without panitumumab for patients with previously untreated advanced oesophagogastric cancer (REAL3): a randomised, open-label phase 3 trial

Tom Waddell, Ian Chau, David Cunningham, David Gonzalez, Alicia Frances, Clare Okines, Andrew Wotherspoon, Claire Saffery, Gary Middleton, Jonathan Wadley, David Ferry, Wasat Mansoor, Tom Crosby, Fareeda Coxon, David Smith, Justin Waters, Timothy Ilveson, Stephen Falk, Sarah Slater, Clare Peckitt, Yolanda Barchechano

Summary
Background EGFR overexpression occurs in 27–55% of oesophagogastric adenocarcinomas, and correlates with poor prognosis. We aimed to assess addition of the anti-EGFR antibody panitumumab to epirubicin, oxaliplatin, and capecitabine (EOC) in patients with advanced oesophagogastric adenocarcinoma.

Lancet Oncol 2013; 14: 485–89
Published Online: April 11, 2013
http://dx.doi.org/10.1016
Anti-angiogenic Therapy

Gastric Cancer

- Preclinical rationale
- Phase II – Studies

AVAGAST

N=774
Stomach and EGJ
Stage IV

Randomized controlled trial

Primary endpoint: survival (superiority)

**Primary endpoint:** survival (superiority)

**Intervention Groups:**
- **Bevacizumab + Cisplatin/Capecitabine q3w**
  - Cis 6 cycles; Bevacizumab + Cape until progression

**Control Group:**
- **Cisplatin/Capecitabine q3w**
  - Cis 6 cycles; Cape until progression

Reference:
AVAGAST

Survival: primary endpoint negative

Kang YK et al. ASCO 2010; LBA 4007
AVAGAST

Disease-free Survival: secondary endpoint positive
Anti-angiogenic Therapy in Gastric Cancer

Conclusions

- The Avagast-Study is a negative trial
- Anti-angiogenic therapy has activity and more potential than AVAGAST shows
- Bevacizumab seems to be active in specific subgroups (tumor genetics, pharmacogenetics, ethnicity…?)
- Randomized controlled trial in the periopeartive setting is ongoing (MAGIC-B)
Anti-angiogenic Treatment with Bevacizumab

Bevacizumab

Gastric Cancer – Biomarker
VEGF-A Levels (Plasma)
AVAGAST Study

Gastric Cancer – Biomarker Neuropilin Expression (Tumor) AVAGAST Study

Anti-angiogenic Treatment with Ramucirumab

Phase I Pharmacologic and Biologic Study of Ramucirumab (IMC-1121B), a Fully Human Immunoglobulin G1 Monoclonal Antibody Targeting the Vascular Endothelial Growth Factor Receptor-2


Purpose
To evaluate the safety, maximum-tolerated dose (MTD), pharmacokinetics (PKs), pharmacodynamics, and preliminary anticancer activity of ramucirumab (IMC-1121B), a fully human immunoglobulin G1 monoclonal antibody targeting the vascular endothelial growth factor receptor (VEGFR)-2.
Ramucirumab (Lilly)

DCE-MRI

Pretreatment

A

B

Post-treatment (Cycle 1)

C

D

Post Gadolinium Injection

Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma ( REGARD ): an international, randomised, multicentre, placebo-controlled, phase 3 trial

Charles S Fuchs, Jiri Tomasek, Cho Jae Yong, Filip Dumitru, Rodolfo Passalacqua, Chanchal Goswami, Howard Safran, Lucas Vieira dos Santos, Giuseppe Aprile, David RFerry, Bohuslav Melichar, Mustapha Tehfe, Eldar Topuzov, John Raymond Zalcberg, Ian Chou, William Campbell, Choondal Sivanandan, Joanna Pikel, Minori Koshiji, Yanzhi Hsu, AstrA M Liepa, Ling Gao, Jonathan D Schwartz, Josep Tabernero, for the REGARD Trial Investigators

Summary
Background Vascular endothelial growth factor (VEGF) and VEGF receptor-2 (VEGFR-2)-mediated signalling and angiogenesis can contribute to the pathogenesis and progression of gastric cancer. We aimed to assess whether ramucirumab, a monoclonal antibody VEGFR-2 antagonist, prolonged survival in patients with advanced gastric cancer.

Methods We did an international, randomised, double-blind, placebo-controlled, phase 3 trial between Oct 6, 2009,
Ramucirumab (REGARD Study)

Randomization 2:1
Primary endpoint: overall survival (superiority)

N=335
Stomach and AEG
Stage IV 2nd-line
119 centers 29 countries

Ramucirumab 8mg/kg q2w until progression
Placebo q2w until progression

Fuchs et al. Lancet Oncol 2013; epub
### Ramucirumab (REGARD Study)

<table>
<thead>
<tr>
<th>Response Type</th>
<th>Ramucirumab (n=238)</th>
<th>Placebo (n=117)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Best overall response</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>1 (&lt;1%)</td>
<td>0</td>
<td>..</td>
</tr>
<tr>
<td>Partial response</td>
<td>7 (3%)</td>
<td>3 (3%)</td>
<td>..</td>
</tr>
<tr>
<td>Stable disease</td>
<td>108 (45%)</td>
<td>24 (21%)</td>
<td>..</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>78 (33%)</td>
<td>63 (54%)</td>
<td>..</td>
</tr>
<tr>
<td>Not evaluable</td>
<td>44 (18%)</td>
<td>27 (23%)</td>
<td>..</td>
</tr>
<tr>
<td>Objective response</td>
<td>8 (3%)</td>
<td>3 (3%)</td>
<td>0.76</td>
</tr>
<tr>
<td>Disease control rate*</td>
<td>116 (49%)</td>
<td>27 (23%)</td>
<td>&lt;0.0001</td>
</tr>
</tbody>
</table>

Data are n (%), unless otherwise indicated. *Denotes best response for complete response, partial response, or stable disease.

**Table 2: Objective tumour response**

Fuchs et al. *Lancet Oncol* 2013; epub
Ramucirumab (REGARD Study)

Median 5.2 versus 3.8 months
Ramucirumab (REGARD Study)

Subgroup analysis
Survival

Fuchs et al. *Lancet Oncol* 2013; epub
Ramucirumab (REGARD Study)

Fuchs et al. Lancet Oncol 2013; epub
Ramucirumab (REGARD Study)

Fuchs et al. Lancet Oncol 2013; epub
# Ramucirumab (REGARD Study)

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab (n=236)</th>
<th>Placebo (n=115)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Any event</td>
<td>Grade ≥3</td>
</tr>
<tr>
<td>Fatigue*</td>
<td>84 (36%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Abdominal pain†</td>
<td>68 (29%)</td>
<td>14 (6%)</td>
</tr>
<tr>
<td>Decreased appetite</td>
<td>57 (24%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>47 (20%)</td>
<td>6 (3%)</td>
</tr>
<tr>
<td>Constipation</td>
<td>36 (15%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Anaemia‡</td>
<td>35 (15%)</td>
<td>15 (6%)</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>25 (11%)</td>
<td>5 (2%)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>22 (9%)</td>
<td>4 (2%)</td>
</tr>
</tbody>
</table>

**Adverse events of special interest**

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension§</td>
<td>38 (16%)</td>
<td>9 (8%)</td>
</tr>
<tr>
<td>Bleeding or haemorrhage¶</td>
<td>30 (13%)</td>
<td>13 (11%)</td>
</tr>
<tr>
<td>Arterial thromboembolism</td>
<td></td>
<td>4 (2%)</td>
</tr>
<tr>
<td>Venous thromboembolism**</td>
<td>9 (4%)</td>
<td>8 (7%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>7 (3%)</td>
<td>3 (3%)</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>2 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Fistula formation</td>
<td>1 (&lt;1%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Infusion-related reaction</td>
<td>1 (&lt;1%)</td>
<td>2 (2%)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

*Fuchs et al. Lancet Oncol 2013; epub*
Lilly Announces Second Positive Ramucirumab Phase III Gastric Cancer Study Meets Primary Endpoint; Phase III Lilly/TRIO Breast Cancer Study Misses Primary Endpoint

-- Additional Phase III Top-Line Results in Other Tumor Types Expected in 2014 --

INDIANAPOLIS, Sept. 26, 2013 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today announced top-line results from two global Phase III studies of ramucirumab (IMC-1121B), one in advanced gastric cancer and another in metastatic breast cancer.

The RAINBOW trial, a global Phase III study of ramucirumab in combination with paclitaxel in patients with advanced gastric cancer, met its primary endpoint of improved overall survival and a secondary endpoint of improved progression-free survival.

The global, randomized, double-blind RAINBOW trial compared ramucirumab and paclitaxel to placebo and paclitaxel in patients with advanced (locally advanced, unresectable or metastatic) gastric cancer that was refractory to or progressive after initial chemotherapy. The most common (> 5% incidence) Grade ≥3 adverse events occurring at a higher rate on the ramucirumab-plus-paclitaxel arm compared to the control arm included neutropenia, leukopenia, hypertension, fatigue/asthenia...
Future Second-line Treatment

Evaluation of ECOG-PS, response to 1st-line CTx and motivation

- ECOG PS 0-1 motivation ++
  - Paclitaxel + Ramucirumab

- EOGG 1-2 motivation +/-
  - Ramucirumab mono

- ECOG 3-4 motivation -
  - ASC
Thank you for your attention!