Novel targets in the treatment of advanced gastric cancer

What exists already and what comes next?

Florian Lordick, MD
Director of the University Cancer Center Leipzig (UCCL)
Professor of Oncology – University of Leipzig
Gastric Cancer – Global Perspective

<table>
<thead>
<tr>
<th>Tumor type</th>
<th>New Cases (million)</th>
<th>Deaths (million)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastro-esophageal cancer</td>
<td>1.4</td>
<td>1.1</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>1.4</td>
<td>1.2</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>1.2</td>
<td>0.4</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>Overall</td>
<td>10.8</td>
<td>7.0</td>
</tr>
</tbody>
</table>

Kamangar et al. *J Clin Oncol* 2006; 24: 2137-2150
Only 10-25% are long-term survivors

Commonly used regimens for GC stage 4

**Doublets**
- Cisplatin-S-1 - Japan
- Cisplatin-5FU - Europe
- Cis-/Oxaliplatin-Capecitabine - Korea
- Oxaliplatin-5FU (FOLFOX) – U.S., Europe
- Irinotecan-5FU (FOLFIRI) - France

**Triplets**
- Epirubicin-Cisplatin-5FU (ECF) and related regimens – UK, NL
- Docetaxel-Cisplatin-5FU (DCF) and related regimens (FLOT) - Europe

**Survival**
- Europe / North America: 8-11 months ; East Asia 11-18 months
Gastric Cancer has Complex Genetics

Gastric Cancer has Complex Genetics

Ciriello G *Nature Genetics* 2013;45:1127-1135
Amplification of Potential „Drug Targets“

**HER2 / EGFR / MET gene amplification**

<table>
<thead>
<tr>
<th>Stage</th>
<th>0</th>
<th>I</th>
<th>IIa/IIb</th>
<th>III</th>
<th>IV</th>
</tr>
</thead>
<tbody>
<tr>
<td>Esophageal</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 319</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Gastric</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>n = 170</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

- **MET**
- **HER2**
- **EGFR**
- **Neg.**

Amplification: Gene-to-copy numeric control probe ratio > 2.2

Lennerz J K et al. *J Clin Oncol* 2011;29:4803-4810
**HER2-positive Gastric Cancer**

- **significant HER2 positivity:** ~ 16%

- **Trastuzumab (Herceptin) in HER2-positive GC in stage IV:**
  
  Survival 16.0 vs. 11.8 months (HR=0.65; 95%CI 0.51-0.83)

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

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*Anti-HER2 antibody Trastuzumab prolongs survival in selected patients!*
Test Algorithm in Stage IV Gastric Cancer

Immunohistochemistry Her2

IHC Score 0/1

IHC Score 2

IHC Score 3

(F)ISH-test Her2

(F)ISH -

(F)ISH +

Platin-Fluoropyrimidine +/- Docetaxel

Trastuzumab + Cisplatin-Fluoropyrimidine

Lordick al. *Gastric Cancer* 2014; 17: 213-225
### Other HER2-directed Approaches in Stage IV

<table>
<thead>
<tr>
<th>HER2 TKI Lapatinib</th>
<th>failed in Phase TYTAN and LOGIC phase 3 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>HER2-HER3 mAB Pertuzumab</td>
<td>under evaluation 1st-line ongoing JACOB phase 3 study</td>
</tr>
<tr>
<td>Trastuzumab-Emtansine (TDM-1)</td>
<td>under evaluation 2nd-line ongoing GATSBY phase 3 study</td>
</tr>
</tbody>
</table>
Anti-HER2 Treatment Neoadjuvant Setting? INNOVATION Study – Europe + Korea

STAGE 1: Randomized phase II « pick-the winner » of two experimental arms 1:2:2 randomization

- CTX only
- CTX + Trastuzumab
- CTX + Trastuzumab + Pertuzumab

STAGE 2: Randomized phase III with best experimental arm of STAGE 1 1:3 randomization

- CTX only
- Chemotherapy + Trastuzumab (+ Pertuzumab)
- IMAGE substudy in selected centers: What is the accuracy of FDG-PET in targeted (antibody) treatment

Primary endpoint: near path. CR

Primary endpoint: 5-year overall survival

Global PI: Dr. AD Wagner, Lausanne
Anti-EGFR – EXPAND and REAL-3 Studies

EXPAND-Study
Cetuximab

REAL-3-Study
Panitumumab


Anti-EGFR not effective in biologically unselected GC patients!
Anti-EGFR – EXPAND Study – EGFR Score

EGFR staining intensity according to Hirsch Score

Targeting the HGF/MET pathway in gastric cancer

The receptor tyrosine kinase MET is the cell surface receptor for hepatocyte growth factor (HGF). HGF-mediated activation of MET results in a complex genetic programme referred to as invasive growth, consisting of a series of processes, including proliferation, invasion, and angiogenesis, that occur under normal physiological conditions during embryonic development and pathologically during oncogenesis. The HGF/MET axis is activated in a range of cancers including gastric cancer, and is associated with an aggressive phenotype and poor prognosis. One approach of pathway-selective anticancer drug development is antagonism of ligand-product added to an established standard chemotherapy regimen. They showed signs of efficacy for the new combination that can now be validated in a prospective controlled phase 3 trial. Additionally, they undertook the challenge of predictive biomarker research, potentially allowing for the identification of a gastric cancer subpopulation with a realistic chance of benefiting from the new drug.

However, some caveats exist. First, the new combination almost did not progress from phase 1b to phase 2 because it was associated with some unpleasant adverse events including one stroke that was thought to...
Farnesyltransferase inhibitor zarnestra reduces induction time of prostate cancer metastases

- PFS hazard ratio 0.6 (95% CI 0.45-0.79, p=0.016) Rilotumumab vs Placebo + ECX
- Stronger efficacy in MET+ tumors (newly developed IHC score)
- Generally well tolerated (but hematological toxicity, edema, thrombosis)
- Phase III ongoing in MET-positive tested Gastric Cancer

Anti-MET inhibitor AMG337– GASTRIC Cancer

FDG-PET Max Intensity Projections

Baseline

Week 5

Green: MET
Red: EGFR
Cyan: Chromosome 7

CT %Δ Sum of Diameters From Baseline

<table>
<thead>
<tr>
<th>Weeks Postdose</th>
<th>%Δ SOD From Baseline</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0%</td>
</tr>
<tr>
<td>5</td>
<td>-10%</td>
</tr>
<tr>
<td>9</td>
<td>-20%</td>
</tr>
<tr>
<td>17</td>
<td>-30%</td>
</tr>
<tr>
<td>25</td>
<td>-40%</td>
</tr>
<tr>
<td>33</td>
<td>-50%</td>
</tr>
<tr>
<td>41</td>
<td>-60%</td>
</tr>
<tr>
<td>49</td>
<td>-70%</td>
</tr>
<tr>
<td>57</td>
<td>-80%</td>
</tr>
<tr>
<td>65</td>
<td>-90%</td>
</tr>
<tr>
<td>73</td>
<td>-100%</td>
</tr>
</tbody>
</table>

Dose | RECIST Response | Prior Therapy | TTP on Prior Therapy
-----|-----------------|---------------|---------------------|
200 mg | CR              | FOLFOX        | 9 weeks             |

Hong D et al. J Clin Oncol 32:5s, 2014 (suppl; abstr 2508)
Anti-Angiogenic Approach

Dr. Judah Folkman, Boston 1933-2008

Folkman’s Hypothesis


http://3quarksdaily.blogs.com/3quarksdaily/images/12folkman_1.jpg
Anti-Angiogenic Approach

Bevacizumab Failed in 1st-line Gastric Cancer

AVAGAST

Survival not significantly improved

## 2nd-line Gastric Cancer – Randomized Studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Survival</th>
<th>Improvement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thuss-Patience et al. EJC 2011, AIO (n=40)</td>
<td>Irinotecan vs. BSC</td>
<td>4.0 Mon vs. 2.4 Mon (p=0.012)</td>
<td>HR 0.48 ∆ 1.6 months</td>
</tr>
<tr>
<td>Kang et al. JCO 2012, Korea (n=202)</td>
<td>Irinotecan or Docetaxel vs. BSC</td>
<td>5.3 Mon vs. 3.8 Mon (p=0.007)</td>
<td>HR 0.657 ∆ 1.5 months</td>
</tr>
<tr>
<td>Ford et al. LANCET ONC 2014, COUGAR-02 (n=168)</td>
<td>Docetaxel vs. BSC</td>
<td>5.2 Mon vs. 3.6 Mon (p=0.001)</td>
<td>HR 0.67 ∆ 1.6 months</td>
</tr>
<tr>
<td>Fuchs et al. LANCET 2014 REGARD (n=223)</td>
<td>Ramucirumab vs. BSC</td>
<td>5.2 Mon vs. 3.8 Mon (p=0.047)</td>
<td>HR 0.776 ∆ 1.4 months</td>
</tr>
</tbody>
</table>
Ramucirumab monotherapy for previously treated advanced gastric or gastro-oesophageal junction adenocarcinoma (REGARD): an international, randomised, multicentre, placebo-controlled, phase 3 trial

Summary
Background Vascular endothelial growth factor (VEGF) and angiogenesis can contribute to the pathology of stomach cancer.

Median: 3.8 vs. 5.2 months

N=335
Stomach / EGJ
Stage IV, 2nd-line after Platin/5FU
119 centers

Fuchs et al., Lancet 2014; 383: 31-9
Response

<table>
<thead>
<tr>
<th></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* 2014; 383: 31-9
Ramucirumab 2nd-line ( REGARD )

Quality of life assessment

Figure 5: Patient-reported global quality of life 6 weeks after start of treatment initiation

Fuchs et al., Lancet 2014; 383: 31-9
Ramucirumab 2nd-line (RAINBOW)

N=665
Stomach and EGJ
Stage IV
2nd-line after Platin/5FU
170 centers
27 countries

Ramucirumab 8mg/kg q2w
Paclitaxel 80 mg/m² d1,8+15 q4w until progression

1:1
Primary endpoint: survival

Placebo q2w
Paclitaxel 80 mg/m² d1,8+15 q4w until progression

Wilke et al., Lancet Oncol 2014; [published online 18 September]
Ramucirumab 2nd-line (RAINBOW)

<table>
<thead>
<tr>
<th></th>
<th>RAM + Paclitaxel</th>
<th>Placebo + Paclitaxel</th>
<th>HR P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Response Rate</td>
<td>28%</td>
<td>16%</td>
<td>p = 0.0001</td>
</tr>
<tr>
<td>PFS (med, Mon)</td>
<td>4.4 22%</td>
<td>2.9 10%</td>
<td>HR 0.635 p &lt; 0.0001</td>
</tr>
<tr>
<td>OS (med, Mon)</td>
<td>9.6 40%</td>
<td>7.3 30%</td>
<td>HR 0.807 p = 0.0169</td>
</tr>
</tbody>
</table>

Wilke et al., *Lancet Oncol* 2014; [published online 18 September]
Evaluation of ECOG-Performance Status, tolerability of 1st-line CTx, patient preference, need for remission

- ECOG 0-1 need for remission++
  - Paclitaxel + Ramucirumab

- ECOG 0-2 need for remission+/-
  - Ramucirumab mono Irinotecan mono Taxan mono

- ECOG 2-4 motivation -
  - Best Supportive Care

Lordick et al., ESMO World Congress GI Cancer 2014
Comprehensive molecular characterization of gastric adenocarcinoma

The Cancer Genome Atlas Research Network

295 gastric adenocarcinomas as part of The Cancer Genome Atlas (TCGA) project

Analyzed for: Mutations, Amplifications, Methylation, miRNA, mRNA, Proteome

Comprehensive Molecular Characterization

4 Subtypes
EBV: Epstein-Barr-Virus +
MSI: Microsatellite instability
GS: Genomically stable
CIN: Chromosomai instability

Comprehensive Molecular Characterization

Immune Checkpoint Inhibition

Immune Checkpoint Inhibition

Gastrointestinal tumours, non-colorectal
Chair(s) C. Verslype (Leuven, Belgium) M. Ducreux (Villejuif, France)
Session Type Proffered Paper session
Details ESMO 2014, 28.09.2014, 09:00 - 10:45, Madrid

LBA15 - A Phase 1b Study of Pembrolizumab (Pembro; MK-3475) in Patients (Pts) With Advanced Gastric Cancer
K. Muro (Nagoya, Japan) Y. Bang (Seoul, Korea) V. Shankaran (Seattle, United States of America)
R. Geva (Tel Aviv, Israel) D. Catenacci (Chicago, United States of America)
S. Gupta (Tampa, United States of America) J. Eder (New Haven, United States of America)
R. Berger (Tel Hashomer, Israel) E. Gonzalez (Rahway, United States of America)
J. Pulini (North Wales, United States of America) A. Ray (Rahway, United States of America)
M. Dolled-Filhart (Rahway, United States of America) K. Emancipator (Rahway, United States of America)
K. Pathiraja (Rahway, United States of America) X. Shu (North Wales, United States of America)
M. Koshiji (Rahway, United States of America) J. Cheng (North Wales, United States of America)
H. Chung (Seoul, Korea)
Stemcellness – „Hallmark of Cancer“

From „Hallmarks of Cancer“ by Hanahan & Weinberg Cell 2011; 144: 646-674
Targeting Cancer Stem Cells

Cancer Stem Cells

Cancer Cell Stemness Inhibitor

Cancer Stem Cells (CSC)
- Highly tumorigenic
- Fundamentally responsible for continued malignant growth
- Initiators (seeds) of metastasis
- Resistant to chemo and current targeted therapies

Heterogeneous Cancer Cells
Targeting Cancer Stem Cells via STAT-3 and beta-catenin pathways

BBI-608: Inhibits Stat3 transcription factor

BBI-608: BRIGHTER randomized controlled phase III study 2nd-line

By courtesy of Bioston Biomedical; http://www.bostonbiomedical.com/index.htm
Conclusions – Gastro-esophageal Cancer

- Poor outcome with chemotherapy in stage 4 – high medical need
- Genetics are complex; high mutational frequencies
- HER2 amplifications: 15-20% → better outcome with Trastuzumab
- Anti-EGFR treatment failed in phase 3
- Anti HGF/MET treatment has promising results in phase 1 + 2
- New molecular characterization is being developed
- May lead to more specific (personalized) treatment
- Immune checkpoint inhibition – first data awaited @ESMO 2014
- Stem cell inhibitors are being studied
Warm regards from Leipzig, Germany!

Creativity

Atmosphere

Commerce

Music

Science