ESMO Preceptorship
Targeted Therapy for Gastric Cancer

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Professor of Oncology
Director University Cancer Center Leipzig (UCCL)
Disclosure

Florian Lordick declares honoraria for advisory role, membership in data safety board or lectures within the last three years for Amgen, Astellas, Astra Zeneca, Biontech, BMS, Ganymed, Elsevier, Excerpta Medica, MSD, Roche, Servier, and Taiho. He receives research support from BMS.
Systemic Treatment Options in GC

Chemotherapy

Molecular Targeted therapy

Anti-angiogenic therapy

Immuno therapy

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## Targeted Therapy in GC – Not a Success Story

<table>
<thead>
<tr>
<th>Compound</th>
<th>Mechanism of action</th>
<th>Treatment setting</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cetuximab</td>
<td>Anti-EGFR mAB</td>
<td>1st-line metastatic</td>
<td>Lordick et al. 2013</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Anti-EGFR mAB</td>
<td>1st-line metastatic</td>
<td>Waddell et al. 2013</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Anti-EGFR TKI</td>
<td>2nd-line metastatic</td>
<td>Petty et al. 2017</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Anti-HER2 mAB</td>
<td>2nd-line metastatic</td>
<td>Makiyama et al. 2018</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Anti-HER2 mAB</td>
<td>1st-line metastatic</td>
<td>Tabernero et al. 2017</td>
</tr>
<tr>
<td>Lapatinib</td>
<td>Anti-EGFR/HER2 TKI</td>
<td>2nd-line metastatic</td>
<td>Satoh et al. 2014</td>
</tr>
<tr>
<td>Rilotumumab</td>
<td>Anti-HGF mAB</td>
<td>1st-line metastatic</td>
<td>Catenacci et al. 2017</td>
</tr>
<tr>
<td>Onartuzumab</td>
<td>Anti-MET mAB</td>
<td>1st-line metastatic</td>
<td>Shah et al. 2017</td>
</tr>
<tr>
<td>Napabucasin</td>
<td>Anti-STAT3</td>
<td>2nd-line metastatic</td>
<td>Shah et al. 2018</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Anti-VEGF mAB</td>
<td>Perioperative</td>
<td>Cunningham et al. 2017</td>
</tr>
<tr>
<td>Bevacizumab</td>
<td>Anti-VEGF mAB</td>
<td>1st-line metastatic</td>
<td>Ohtsu et al. 2011</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>Anti-VEGFR-2 mAB</td>
<td>1st-line metastatic</td>
<td>Fuchs et al. 2018</td>
</tr>
<tr>
<td>Olaparib</td>
<td>PARP inhibitor</td>
<td>2nd-line metastatic</td>
<td>Bang et al. 2017</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1-directed mAB</td>
<td>2nd-line metastatic</td>
<td>Shitara et al. Lancet 2018</td>
</tr>
</tbody>
</table>
Potential Molecular Targets in Gastric Cancer

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).

Potential Molecular Targets in Gastric Cancer

**Anti-EGFR**

negative phase-3: EXPAND, REAL3
Lordick et al. Lancet Oncol 2013
Waddell et al. Lancet Oncol 2013

**Anti-MET**

negative phase-3: MetMab, RiloMet
Shah et al. ASCO 2015
Cunningham et al. ASCO 2015

**anti-FGFR**

preliminary phase-2: Shine
Bang et al. ASCO 2015

**KRAS**

non druggable (?)

**HER2**

positive phase-3: ToGA
Bang et al. Lancet 2010

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)

mixed, 3+

intestinal, 0-3+

diffuse, 2+

diffuse, 1+

Gamboa et al. *Mod Pathol* 2004;17:579-87
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></th>
<th>n</th>
<th>Response (%)</th>
<th>mTTP (Mon)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FUFOX + Cetuximab</td>
<td>46</td>
<td>65%</td>
<td>7.6</td>
</tr>
<tr>
<td>Lordick F, et al. BJC 2010</td>
<td></td>
<td>95% CI, 50–79%</td>
<td>95% CI, 5.0–10.1</td>
</tr>
</tbody>
</table>

### EXPAND Study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose and Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cisplatin</td>
<td>80mg/m² d1</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>1000mg/m² 2 x / day.; d1-14 q3w</td>
</tr>
<tr>
<td>Cetuximab</td>
<td>400mg/m² loading dose, then 250mg/m² / week</td>
</tr>
</tbody>
</table>

- Until radiographic progression or toxicity-related end of treatment
- Primary endpoint: Progression-free survival (PFS)

**Lordick et al.,** *Lancet Oncol.* 2013; 14: 490-499
EXPAND Study

Lordick et al., Lancet Oncol. 2013; 14: 490-499
Pre-EXPAND Study

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

EGFR (red), chromosome 7 (green)

Luber B,… Lordick F. BMC Cancer 2011;11:509
### EXPAND Study

<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>

What Can We Learn from the EGFR Lesson?

• A good study hypothesis is important: preclinical evidence…

• Do not trust in overoptimistic phase II data

• Do correlative research and explore biomarkers!

• For rare subtypes of cancer - you need a strong network!
Anti-HER2 Trastuzumab prolongs survival in stage IV gastric cancer

Survival advantage with trastuzumab in HER2+ gastric cancer


CI, confidence interval; HER2, human epidermal growth factor receptor 2; HR, hazard ratio.

**Gastric Cancer Therapy in Stage IV**

**Treatment of advanced gastroesophageal cancer**
Molecular stratification according to HER2 status

- IHC score 0/1
  - Platin-fluoropyrimidine +/− docetaxel or epirubicin

- IHC score 2
  - ISH-test HER2
    - ISH−
      - Platin-fluoropyrimidine +/− docetaxel or epirubicin
    - ISH+
      - Cisplatin-fluoropyrimidine + trastuzumab

- IHC score 3

**HER2**, human epidermal growth factor receptor 2;
**IHC**, immunohistochemistry; **ISH**, in situ hybridisation.

The mechanism of action of pertuzumab and trastuzumab. Trastuzumab binds to the ECD IV of the HER2 receptor, preventing the spontaneous formation of homodimers (HER2–HER2) and ligand-independent heterodimers (HER2–HER3 and also HER2–HER1 and HER2–HER4). Pertuzumab binds to the dimerization domain of the HER2 receptor (ECD II), preventing the formation of ligand-induced HER2 heterodimers.

**Pertuzumab – Trastuzumab – JACOB Study**

**Number at risk (number censored)**

<table>
<thead>
<tr>
<th></th>
<th>Pertuzumab group</th>
<th>Control group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A (n=388)</td>
<td>388 (10)</td>
<td>392 (9)</td>
</tr>
<tr>
<td>Arm B (n=392)</td>
<td>363 (34)</td>
<td>359 (11)</td>
</tr>
<tr>
<td></td>
<td>342 (12)</td>
<td>339 (13)</td>
</tr>
<tr>
<td></td>
<td>323 (14)</td>
<td>306 (15)</td>
</tr>
<tr>
<td></td>
<td>297 (15)</td>
<td>279 (15)</td>
</tr>
<tr>
<td></td>
<td>266 (17)</td>
<td>252 (16)</td>
</tr>
<tr>
<td></td>
<td>243 (15)</td>
<td>221 (16)</td>
</tr>
<tr>
<td></td>
<td>209 (15)</td>
<td>175 (16)</td>
</tr>
<tr>
<td></td>
<td>175 (35)</td>
<td>143 (31)</td>
</tr>
<tr>
<td></td>
<td>149 (49)</td>
<td>118 (42)</td>
</tr>
<tr>
<td></td>
<td>114 (75)</td>
<td>95 (69)</td>
</tr>
<tr>
<td></td>
<td>92 (86)</td>
<td>76 (86)</td>
</tr>
<tr>
<td></td>
<td>67 (91)</td>
<td>60 (91)</td>
</tr>
<tr>
<td></td>
<td>54 (101)</td>
<td>47 (101)</td>
</tr>
<tr>
<td></td>
<td>36 (108)</td>
<td>38 (108)</td>
</tr>
<tr>
<td></td>
<td>27 (117)</td>
<td>31 (117)</td>
</tr>
<tr>
<td></td>
<td>16 (123)</td>
<td>14 (123)</td>
</tr>
<tr>
<td></td>
<td>10 (126)</td>
<td>7 (126)</td>
</tr>
<tr>
<td></td>
<td>6 (128)</td>
<td>4 (128)</td>
</tr>
<tr>
<td></td>
<td>4 (242)</td>
<td>3 (242)</td>
</tr>
</tbody>
</table>

**Overall survival (%)**

- **Arm A (n=388)**
- **Arm B (n=392)**

**mPFS, months**

<table>
<thead>
<tr>
<th></th>
<th>Arm A (n=388)</th>
<th>Arm B (n=392)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS, months</td>
<td>8.5</td>
<td>7.0</td>
<td>0.73 (0.62, 0.86)</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>56.7</td>
<td>48.3</td>
<td>Difference 8.4 (0.9, 15.9)</td>
</tr>
</tbody>
</table>

**Tabernero J et al.** Lancet Oncol. 2018 Sep 11. [Epub ahead of print]
Heterogenous / focal HER-2 – expression in gastric cancer

HER2-Testing Central and Local

VARIANZ-Study
549 patients with advanced gastric cancer enrolled
Target 50 pts with HER2-positive gastric cancer treated with chemoTx + trastuzumab

Patient gives informed consent

1st visit
Start 1st line treatment

2nd visit
12 months

3rd visit
24 months

Tumor tissue to central pathology Leipzig

HER2 Immunohistochemistry

HER2 amplification

HER2 positive:
IHC3+; IHC2+ & CISH+

HER2 negative:
IHC0, IHC1+, IHC2+ & CISH-
(according to criteria ToGA-study)

Lordick et al. AACR, Chicago, 2018 abstract
HER2 Testing Central and Local

HER2 central test

491 pts have been tested by central pathology
- green: 85 pts with HER2 positive GC
- blue: 406 pts with HER2 negative GC

Deviation rate 23%

Lordick et al. AACR, Chicago, 2018 abstract
Trastuzumab treatment

- **green**: 85 HER2 positive: 61 receive trastuzumab
- **blue**: 406 HER2 negative: 58 receive trastuzumab

Lordick et al. AACR, Chicago, 2018 abstract
Gastric Cancer Therapy in Stage IV

Treatment of advanced gastroesophageal cancer
Molecular stratification according to HER2 status

- **IHC score 0/1**
  - Platin-fluoropyrimidine +/– docetaxel or epirubicin

- **IHC score 2**
  - **ISH-test HER2**
    - **ISH−**
    - **ISH+**

- **IHC score 3**
  - Cisplatin-fluoropyrimidine + trastuzumab

HER2, human epidermal growth factor receptor 2; IHC, immunohistochemistry; ISH, in situ hybridisation.

2nd-line HER2-targeted treatment?

A randomized phase II study of weekly paclitaxel ± trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G (T-ACT)

Akira Makiyama1, Kosuke Sagarase1, Junji Kawada1, Tomomi Kashwada1, Ayumu Hosokawa1, Yoshiki Horie1, Hiroaki Saito1, Yoshiyuki Yamamoto1, Hiroaki Taniguchi1, Katsunori Shinozaki1, Kazuhiko Nishikawa1, Keita Uchino1, Yasutaka Suzuki1, Takeharu Yamanaka1, Kentaro Yamauchi1, Shuichi Hirose1, Nanikatu Boku1, Ichinosuke Hiyodo1, Teruo Esaka1, Kei Muro1


Study schema and Treatment

T-ACT study: Trial to Assess the Concept of TBP

HER2-positive advanced G/GEJ adenocarcinoma refractory to 1st-line chemotherapy with fluoropyrimidine, platinum, and Tmab

Stratification factor: Institution, ECOG PS 0–1/2, IHC3+ / IHC2+ & FISH+, Target lesion +/-

Endpoints and Statistical design

Primary endpoint: progression-free survival (PFS)

Makiyama et al. ASCO 2018; #4011
A randomized phase II study of weekly paclitaxel ± trastuzumab in patients with HER2-positive advanced gastric or gastro-esophageal junction cancer refractory to trastuzumab combined with fluoropyrimidine and platinum: WJOG7112G (T-ACT)

Makiyama et al. ASCO 2018; #4011
2nd-line HER2-targeted treatment?

Pre-trastuzumab (HER2+)
- H&E
- HER2 IHC
- PIK3CA WT
- PIK3CA E454K Mutation

Post-trastuzumab (HER2-)
- H&E
- HER2 IHC
- ERBB2 FISH

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Janjigian Y et al.. Cancer Discovery 2018 Jan;8(1):49-58
Tumor Heterogeneity and Evolution

- Tumor Heterogeneity
- Biological Evolution
- Treatment Resistance
RESEARCH BRIEF

Genomic Heterogeneity as a Barrier to Precision Medicine in Gastroesophageal Adenocarcinoma

Eirini Pectasides1,2, Matthew D. Stachler1,3, Sarah Derks1,4, Yang Liu1,5, Steven Maron6, Mirazul Islam1,5, Lindsay Alpert7, Heewon Kwak7, Hedy Kindler6, Blase Polite6, Manish R. Sharma6, Kenisha Allen6, Emily O’Day6, Samantha Lomnicki6, Melissa Maranto6, Rajani Kanteti6, Carrie Fitzpatrick7, Christopher Weber7, Namrata Setia7, Shu-Yuan Xiao7, John Hart7, Rebecca J. Nagy8, Kyoung-Mee Kim9, Min-Gew Choi10, Byung-Hoon Min11, Katie S. Nason12, Lea O’Keefe12, Masayuki Watanabe13, Hideo Baba14, Rick Lanman8, Agoston T. Agoston3, David J. Oh15, Andrew Dunford5, Aaron R. Thorner16, Matthew D. Ducar16, Bruce M. Wollison16, Haley A. Coleman16, Yuan Ji17, Mitchell C. Posner18, Kevin Roggin18, Kiran Turaga18, Paul Chang19, Kyle Hogarth20, Uzma D. Siddiqui21, Andres Gelrud21, Gavin Ha5, Samuel S. Freeman5, Justin Rhoades5, Sarah Reed5, Greg Gydush5, Denisse Rotem5, Jon Davison12, Yu Imamura13,14, Viktor Adalsteinsson5, Jeeyun Lee22, Adam J. Bass1,5, and Daniel V. Catenacci6

Pectasides et al. Cancer Discovery 2017; 8: 1–12
Tumor Heterogeneity in GC

A
Cohort 1: 11 patients
whole-exome sequencing

Distant metastasis
Primary

B
Gene mutations
22% in primary only
58% shared
19% in metastasis only

Gene amplifications
32% in primary only
37% shared
31% in metastasis only

Pectasides et al. Cancer Discovery 2017; 8: 1–12
Tumor Heterogeneity in GC

PANGEA trial
28 patients

Distant metastasis

Cell-free DNA

Primary

Guardant 360 targeted sequencing

Foundation Medicine targeted sequencing

Treatment assignment

No discordance between primary and metastasis requiring change in treatment assignment

32%

Biomarker discordance between primary and metastasis led to treatment reassignment

68%

Pectasides et al. Cancer Discovery 2017; 8: 1–12
Figure 3. Changes in Clonal Composition over Time, Estimated on the Basis of Changes in Clonal-Mutation Prevalence.

Cellular clones with a common genotype are shown in the same color. The abundance of genotypes is estimated over time or space with sequencing methods. Large changes in the abundance of specific clones may give clues as to which genotypes may confer resistance and which may be sensitive to some intervention. This requires that the rate of clonal expansion or decline under nonselective conditions can be estimated or reasonably assumed to be similar among clones.
Tumor Heterogeneity and Evolution

Resection, adjuvant Drug A  Drug B (Metastases)
Liquid Biopsy

Anti-Angiogenic Approach

Dr. Judah Folkman, Boston 1933–2008

Folkman’s Hypothesis

http://3quarksdailyblogs.com/3quarksdailyimages/12folkman_1.jpg

Anti-Angiogenic Approach

### Ramucirumab 2nd-line Mono (REGARD)

<table>
<thead>
<tr>
<th></th>
<th>RAM + BSC</th>
<th>Placebo + BSC</th>
<th>HR</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease Control</td>
<td>49%</td>
<td>23%</td>
<td>P</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PFS (med, Mon)</td>
<td>2.1</td>
<td>1.3</td>
<td>HR</td>
<td>0.48</td>
</tr>
<tr>
<td></td>
<td>p &lt;0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS (med, Mon)</td>
<td>5.2</td>
<td>3.8</td>
<td>HR</td>
<td>0.78</td>
</tr>
<tr>
<td></td>
<td>p =0.047</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

5FU, fluorouracil; CI, confidence interval; EGJ, oesophageal junction; HR, hazard ratio.

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Ramucirumab 2nd-line Mono

Median OS (months) by Study Arm

REGARD: Ramucirumab vs PBO (BSC) (n=355)
- Active Treatment: 5.2
- BSC: 3.8

UK: COUGAR-02: Docetaxel vs BSC\(^1\) (n=131)
- Active Treatment: 5.2
- BSC: 3.6

Korea: CTX [Docetaxel or Irinotecan] vs BSC\(^2\) (n=202)
- Active Treatment: 5.3
- BSC: 3.8

German: Irinotecan vs BSC\(^3\) (n=40)
- Active Treatment: 4.0
- BSC: 2.4

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## Ramucirumab 2nd-line Combined (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</td>
<td>2.9</td>
<td>HR 0.635</td>
</tr>
<tr>
<td>6 months (%)</td>
<td>22%</td>
<td>10%</td>
<td>p &lt; 0.0001</td>
</tr>
<tr>
<td>OS (med, Mon)</td>
<td>9.6</td>
<td>7.3</td>
<td>HR 0.807</td>
</tr>
<tr>
<td>6 months</td>
<td>40%</td>
<td>30%</td>
<td>p = 0.0169</td>
</tr>
</tbody>
</table>

Ramucirumab 2nd-line Quality of Life (RAINBOW)

Cl, confidence interval; HR, hazard ratio; PBO, placebo; PTX, paclitaxel; RAM, ramucirumab

Is Ramucirumab Effective in HER2 Positive Cancers?

Post-hoc analysis from Regard

Ramucirumab in the Elderly Population?

 REGARD STUDY

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Ramucirumab group</th>
<th>Placebo group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;65</td>
<td>156</td>
<td>71</td>
<td>0.846 (0.611-1.171)</td>
</tr>
<tr>
<td>≥65</td>
<td>82</td>
<td>46</td>
<td>0.722 (0.471-1.106)</td>
</tr>
<tr>
<td>Overall</td>
<td>238</td>
<td>117</td>
<td>0.776 (0.603-0.998)</td>
</tr>
</tbody>
</table>


 RAINBOW STUDY

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Ramucirumab+ paclitaxel</th>
<th>Placebo+ paclitaxel</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>330</td>
<td>335</td>
<td>0.807 (0.678-0.962)</td>
</tr>
<tr>
<td>&lt;65</td>
<td>204</td>
<td>212</td>
<td>0.753 (0.604-0.939)</td>
</tr>
<tr>
<td>≥65</td>
<td>126</td>
<td>123</td>
<td>0.861 (0.636-1.165)</td>
</tr>
</tbody>
</table>

Ramucirumab in the Peritoneal Carcinosis?

**REGARD STUDY**

<table>
<thead>
<tr>
<th>Peritoneal</th>
<th>Ramucirumab group</th>
<th>Placebo group</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>64</td>
<td>45</td>
<td>0.871 (0.556-1.366)</td>
</tr>
<tr>
<td>No</td>
<td>174</td>
<td>72</td>
<td>0.800 (0.582-1.101)</td>
</tr>
<tr>
<td>Overall</td>
<td>238</td>
<td>117</td>
<td>0.776 (0.603-0.998)</td>
</tr>
</tbody>
</table>

**RAINBOW STUDY**

<table>
<thead>
<tr>
<th>Metastasis</th>
<th>Ramucirumab+ paclitaxel</th>
<th>Placebo+ paclitaxel</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>330</td>
<td>335</td>
<td>0.807 (0.678-0.962)</td>
</tr>
<tr>
<td>Peritoneal</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>163</td>
<td>152</td>
<td>0.807 (0.627-1.038)</td>
</tr>
<tr>
<td>No</td>
<td>167</td>
<td>183</td>
<td>0.758 (0.589-0.976)</td>
</tr>
</tbody>
</table>

Anti-Angiogenic Treatment in Early Gastric Cancer or 1st-Line Metastatic GC: not effective

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Drug</th>
<th>Control (C)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>STO-3</td>
<td>Peri-operative</td>
<td>BEV+C</td>
<td>ECX</td>
<td>1</td>
</tr>
<tr>
<td>AVAGAST</td>
<td>1st-line metastatic</td>
<td>BEV+C</td>
<td>CF</td>
<td>2</td>
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<tr>
<td>AVATAR</td>
<td>1st-line metastatic</td>
<td>BEV+C</td>
<td>XP</td>
<td>3</td>
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<tr>
<td>NCT 01246960</td>
<td>1st-line metastatic</td>
<td>RAM+C</td>
<td>FOLFOX</td>
<td>4</td>
</tr>
<tr>
<td>RAINFALL</td>
<td>1st-line metastatic</td>
<td>RAM+C</td>
<td>CF</td>
<td>5</td>
</tr>
<tr>
<td>RAINSTORM</td>
<td>1st-line metastatic</td>
<td>RAM+C</td>
<td>SOX</td>
<td>9</td>
</tr>
</tbody>
</table>

Bev: Bevacizumab  
C: Control  
CF: Cisplatin, 5-Fluorouracil  
ECX: Epirubicin, Cisplatin, Capecitabine  
FOLFOX: Folinic Acid, 5-Fluorozracil, Oxaliplatin  
SOX: S-1, Oxaliplatin  
XP: Capecitabine, Cisplatin

5. Fuchs C et al. ASCO-GI 2018; abstract #5  
6. Muro K. Et al. ASCO 2018; abstract #4038
# Anti-Angiogenic Treatment Among Treatment Lines

## Stomach Cancer

- **Disease setting**: Localized or Adjuvant
- **Impact in OS**: ○
- **Impact in PFS**: △
- **No Impact in OS/DFS/PFS**: ×

<table>
<thead>
<tr>
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</tr>
</thead>
<tbody>
<tr>
<td>Perioperative</td>
<td>○</td>
<td>×</td>
<td>△</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>○</td>
<td>○</td>
<td>△</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>○</td>
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</tbody>
</table>

## Colorectal Cancer

- **Disease setting**: Metastatic and Mostly Palliative
- **Impact in OS**: ○
- **Impact in PFS**: △
- **No Impact in OS/DFS/PFS**: ×

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</tr>
</thead>
<tbody>
<tr>
<td>Perioperative</td>
<td>○</td>
<td>×</td>
<td>×</td>
<td>○</td>
<td>○</td>
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<td>○</td>
<td>○</td>
<td>○</td>
</tr>
<tr>
<td>Locally advanced</td>
<td>○</td>
<td>○</td>
<td>○</td>
<td>△</td>
<td>○</td>
<td>○</td>
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<td>○</td>
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<td>○</td>
</tr>
</tbody>
</table>

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Yoon HH, *ASCO-GI* 2015, substantially modified by Muro K
Progression: evaluation of ECOG performance status, efficacy and tolerability of first-line chemotherapy, patient preferences and the need for remission

- ECOG PS 0–1 need for remission ++: Paclitaxel + ramucirumab
- ECOG PS 0–2 need for remission +/-: Ramucirumab monotherapy or irinotecan monotherapy or taxane monotherapy
- ECOG PS 2–4 or patient preference: Active symptom control

ECOG, Eastern Cooperative Oncology Group; PS, performance status.

Summary

• *Gastric cancer* is a heterogenous disease, which compromises - to a certain extent – targeted treatment

• *Trastuzumab* plus chemo-doublet improves survival in first-line metastatic gastric cancer

• Other *receptor tyrosine kinase* directed treatments have failed thus far

• *Ramucirumab* alone and - even more - *ramucirumab plus paclitaxel* improves survival in 2nd-line gastric cancer
Welcome

Dear Participants of the International Gastric Cancer Congress 2019,

With great pleasure we announce the 2019 International Gastric Cancer Congress to be held in Prague. Gastric Cancer continues to be a major health problem in Europe, in the Asian-Pacific Region, in America, Middle East and Africa. From a worldwide perspective, almost 1 Mio patients are diagnosed with gastric cancer / year and 750.000 die from this aggressive cancer.

http://www.igcc2019-prague.org
Perioperative anti-HER2 Therapy

**TRIGGER study**

HER2 + GC, Bulky N

- SP
  - Surgery
  - S-1
- SP / Tmab
  - Surgery
  - S-1

**Sample size:** 130 pts.
**Primary endpoint:** Overall survival
**Secondary endpoint:** Progression-free survival, response rate, completion of protocol treatment, adverse event

Legend: SP, S-1 plus Cisplatin; Tmab, Trastuzumab
INNOVATION study

HER2-positive mGC or GEJ adenocarcinoma (N = 220) Centrally confirmed Stages IB-III

R 1:2:2

XC or FLOT 3 / 4 cycles (N = 44)

Chemo + T 3 cycles (N = 88)

Chemo + TP 3 cycles (N = 88)

Surgery

XC or FLOT 3 / 4 cycles

Chemo + T 3 cycles

Chemo + TP 3 cycles

T for up to 1 year

TP for up to 1 year

T: Trastuzumab; P: Pertuzumab

- **Primary endpoint:** histopathological near complete response (<10% viable tumour cells) after neoadjuvant therapy

- **Stratification:** histological subtype (intestinal/non-intestinal); Korea versus Europe; stage II versus III; node positive versus node negative