ESMO Preceptorship
Targeted Therapy for Gastric Cancer

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

Personal financial interests (lecture honoraria, advisory boards, travel support)


Institutional financial interests (research support)

- BMS

Leadership roles

- German Cancer Society (Secretary), EORTC (Chairman of the GI Tract Cancer Group), ESMO (GI Faculty Coordinator, Director of Education Elect), International Gastric Cancer Association (President)
Systemic Treatment Options in GC

- **Chemotherapy**
- **Molecular Targeted therapy**
- **Anti-angiogenic therapy**
- **Immuno therapy**
## Targeted Therapy in GC – Not Always 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>1&lt;sup&gt;st&lt;/sup&gt;-line metastatic</td>
<td>Lordick et al. 2013</td>
</tr>
<tr>
<td>Panitumumab</td>
<td>Anti-EGFR mAB</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-line metastatic</td>
<td>Waddell et al. 2013</td>
</tr>
<tr>
<td>Gefitinib</td>
<td>Anti-EGFR TKI</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line metastatic</td>
<td>Petty et al. 2017</td>
</tr>
<tr>
<td>Trastuzumab</td>
<td>Anti-HER2 mAB</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line metastatic</td>
<td>Makiyama et al. 2018</td>
</tr>
<tr>
<td>Pertuzumab</td>
<td>Anti-HER2 mAB</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-line metastatic</td>
<td>Tabernero et al. 2017</td>
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<tr>
<td>Lapatinib</td>
<td>Anti-EGFR/HER2 TKI</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line metastatic</td>
<td>Satoh et al. 2014</td>
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<td>Satoh et al. 2014</td>
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<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>1&lt;sup&gt;st&lt;/sup&gt;-line metastatic</td>
<td>Ohtsu et al. 2011</td>
</tr>
<tr>
<td>Ramucirumab</td>
<td>Anti-VEGFR-2 mAB</td>
<td>1&lt;sup&gt;st&lt;/sup&gt;-line metastatic</td>
<td>Fuchs et al. 2018</td>
</tr>
<tr>
<td>Olaparib</td>
<td>PARP inhibitor</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line metastatic</td>
<td>Bang et al. 2017</td>
</tr>
<tr>
<td>Pembrolizumab</td>
<td>PD-1-directed mAB</td>
<td>2&lt;sup&gt;nd&lt;/sup&gt;-line metastatic</td>
<td>Shitara et al. Lancet 2018</td>
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</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)

RTK gene copy number gains/losses in the patient cohort and cell models.

The EGFR Story

Gamboa et al. Mod Pathol 2004;17:579-87

mixed, 3+

intestinal, 0-3+

diffuse, 2+
diffuse, 1+
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><strong>Lordick F, et al. BJC 2010</strong></td>
<td><strong>46</strong></td>
<td><strong>65%</strong></td>
<td><strong>7,6</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td>95% CI, 50–79%</td>
<td>95% CI, 5.0–10.1</td>
</tr>
</tbody>
</table>

EXPAND Study

Cisplatin 80mg/m² d1
Capecitabine 1000mg/m² 2 x / day.; d1-14 q3w

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

Cisplatin 80mg/m² d1
Capecitabine 1000mg/m² 2 x tgl.; d1-14 q3w
Cetuximab 400mg/m² loading dose, then 250mg/m² / week

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)

---

Log-rank $P=0.011$

**Survival (%)**

- **EGFR FISH $\geq 4.0$**
  - $n=8$

- **EGFR FISH $< 4.0$**
  - $n=28$

**Overall survival time (days)**

---

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 / biological plausibility is important
- Do not trust in overoptimistic phase II data
- Do correlative research and explore biomarkers!
- For rare subtypes of cancer - you need a strong network!
The Cancer Genome Atlas

Four subtypes
- **CIN**: Chromosomal Instability
- **GS**: Genomically stable
- **MSI**: Microsatellite Instability
- **EBV**: Epstein-Barr-Virus

The Cancer Genome Atlas

Four subtypes
- **CIN**: Chromosomal Instability
- **GS**: Genomically stable
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The Cancer Genome Atlas

Four subtypes
- **CIN**: Chromosomal Instability
- **GS**: Genomically stable
- **MSI**: Microsatellite Instability
- **EBV**: Epstein-Barr-Virus

**Anti-HER2 Trastuzumab** prolongs survival in stage IV gastric cancer

- Therapeutically relevant HER2 overexpression: ~ 16%
- Intestinal > diffuse subtype
- Proximal > distal Tumors

**Bang Y,…Lordick F. et al.** *Lancet* 2010;376:687–97
HER2-directed Therapy: ToGA

<table>
<thead>
<tr>
<th>Category</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>0.74 (0.60–0.91)</td>
<td>584</td>
<td>13.8 vs 1.1</td>
<td></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>0.92 (0.48–1.76)</td>
<td>61</td>
<td>10.6 vs 7.2</td>
<td></td>
</tr>
<tr>
<td>IHC 1+/FISH positive</td>
<td>1.24 (0.70–2.20)</td>
<td>70</td>
<td>8.7 vs 10.2</td>
<td></td>
</tr>
<tr>
<td>IHC 2+/FISH positive</td>
<td>0.75 (0.51–1.11)</td>
<td>159</td>
<td>12.3 vs 10.8</td>
<td></td>
</tr>
<tr>
<td>IHC 3+/FISH positive</td>
<td>0.58 (0.41–0.81)</td>
<td>256</td>
<td>17.9 vs 12.3</td>
<td></td>
</tr>
<tr>
<td>IHC 3+/FISH negative</td>
<td>0.83 (0.20–3.38)</td>
<td>15</td>
<td>17.5 vs 17.7</td>
<td></td>
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<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>1.07 (0.70–1.62)</td>
<td>131</td>
<td>10.0 vs 8.7</td>
<td></td>
</tr>
<tr>
<td>IHC 2+/FISH positive or IHC 3+</td>
<td>0.65 (0.51–0.83)</td>
<td>446</td>
<td>16.0 vs 11.8</td>
<td></td>
</tr>
</tbody>
</table>

Favours trastuzumab plus chemotherapy  Favours chemotherapy alone

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.

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

Target Expression in Gastric Cancer

Heterogenous / focal HER-2 – expression in gastric cancer

Loss of Target Expression

Pre-trastuzumab (HER2+)

Post-trastuzumab (HER2-)

PIK3CA WT

PIK3CA E454K Mutation

Janjigian Y et al.. *Cancer Discovery* 2018 Jan;8(1):49-58
2nd-line HER2-targeted treatment?

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)

Progression-free Survival

<table>
<thead>
<tr>
<th></th>
<th>PTX  (n=45)</th>
<th>PTX + Tmab (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months (95% CI)</td>
<td>3.19 (2.86-3.48)</td>
<td>3.68 (2.76-4.53)</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>0.906 (0.674-1.219)</td>
<td>0.334</td>
</tr>
<tr>
<td>P-value (stratified log-rank test)</td>
<td></td>
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</table>

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>PTX  (n=45)</th>
<th>PTX + Tmab (n=44)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, months (95% CI)</td>
<td>9.95 (7.56-13.08)</td>
<td>10.20 (7.85-12.75)</td>
</tr>
<tr>
<td>Stratified HR (95% CI)</td>
<td>1.230 (0.759-1.991)</td>
<td>1.99</td>
</tr>
<tr>
<td>P-value (stratified log-rank test)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Makiyama et al. ASCO 2018; #4011
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

Tumor Heterogeneity

Biological Evolution

Treatment Resistance
Tumor Heterogeneity in GC

A
Cohort 1: 11 patients
whole-exome sequencing

B
Gene mutations
Gene amplifications

- 22% in primary only
- 58% shared
- 19% in metastasis only
- 32% in primary only
- 37% shared
- 31% in metastasis only

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

A

PANGEA trial
28 patients

Distant metastasis

Cell-free DNA

Guardant 360 targeted sequencing

Primary

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

32%

68%

Pangeas et al. Cancer Discovery 2017; 8: 1–12
Tumor Heterogeneity and Evolution

- Baseline Sampling
- Relapse
- Progression

Resection, adjuvant Drug A  Drug B (Metastases)

© University Cancer Center Leipzig (UCCL): Prof. Dr. Florian Lordick
Liquid Biopsy

Diaz et al. *J Clin Oncol* 2014; 32: 579-86
CtDNA follow-up in lapatinib treated GC patients in correlation to radiologic assessment

Kim ST et al. Annals of Oncology 29: 1037–1048, 2018
Tumor Genomic Profiling Guides Patients with Metastatic Gastric Cancer to Targeted Treatment: The VIKTORY Umbrella Trial

Jeeyun Lee¹, Seung Tae Kim¹, Kyung Kim¹, Hyuk Lee², Iwanka Kozarewa³, Peter G.S. Mortimer⁴, Justin I. Odegaard⁵, Elizabeth A. Harrington³, Juyoung Lee¹, Taehyang Lee¹, Sung Yong Oh⁶, Jung-Hun Kang⁷, Jung Hoon Kim⁸, Youjin Kim⁹, Jun Ho Ji⁹, Young Saing Kim¹⁰, Kyoung Eun Lee¹¹, Jinchul Kim¹, Tae Sung Sohn¹², Ji Yeong An¹², Min-Gew Choi¹², Jun Ho Lee¹², Jae Moon Bae¹², Sung Kim¹², Jae J. Kim², Yang Won Min², Byung-Hoon Min², Nayoung K.D. Kim¹³,⁴, Sally Luke³, Young Hwa Kim⁴, Jung Yong Hong¹, Se Hoon Park¹, Joon Oh Park¹, Young Suk Park¹, Ho Yeong Lim¹, AmirAli Talasaz⁵, Simon J. Hollingsworth¹⁴, Kyoung-Mee Kim¹⁵, and Won Ki Kang¹

VIKTORY Trial

Patients with metastatic GC

Enrolled for VIKTORY screening
56.4% at the time of 1st-line chemotherapy
43.6% during or at the time of failure to 1st-line chemotherapy

Tumor pathologic–genomic profiling:
1) Targeted tumor sequencing
2) NanoString (MEK signature)
3) IHC panel: MMR, EBV status, PD-L1, c-MET
4) Serial ctDNA sequencing

Biomarker A1: RAS mt or amp
Biomarker A2: MEK sig high or low
Biomarker B: TP53 mutation
Biomarker C: PIK3CA mt or amp
Biomarker D: MET amp
Biomarker E: MET 3+ by IHC
Biomarker F: All negative
Biomarker G: TSC2 null/RICTOR amp

Arm 1: PII Selumetinib + docetaxel
Arm 2: PII Adavosertib + paclitaxel
Arm 3: PII Capivasertib + paclitaxel
Arm 4: PII Savolitinib
Arm 5: PI/II Savolitinib + paclitaxel
Arm 6: PII Vistusertib + paclitaxel
Arm 7: PII Capivasertib + paclitaxel
Arm 8: PII AZD6738 + paclitaxel
Arm 9*: Vistusertib + paclitaxel
Arm 10**: Vistusertib + paclitaxel


© University Cancer Center Leipzig (UCCL): Prof. Dr. Florian Lordick
Arm 4: savolitinib (MET inhibitor) monotherapy arm for patients with MET-amplified gastric cancer. * indicates newly developed lesion per RECIST 1.1.

VIKTORY Trial

Progression-free survival

\( P < 0.0001 \)

- Conventional chemotherapy \((n = 266)\)
- Biomarker-driven treatment \((n = 105)\)

Claudin 18.2

- Member of the claudin family
- Major structural component of tight junctions
- Seals intercellular space in epithelial sheets
- Not expressed in any healthy tissues, except: stomach mucosa, but with limited accessibility

<table>
<thead>
<tr>
<th>Tissue</th>
<th>Total</th>
<th>Any positivity [%]</th>
<th>≥2+ &gt;40% [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gastric adenocarcinomas</td>
<td>1205</td>
<td>977</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td></td>
<td>603</td>
<td>50</td>
</tr>
<tr>
<td>Diffuse</td>
<td>358</td>
<td>320</td>
<td>89</td>
</tr>
<tr>
<td>Intestinal</td>
<td>395</td>
<td>287</td>
<td>73</td>
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<tr>
<td>Mixed</td>
<td>64</td>
<td>49</td>
<td>77</td>
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<tr>
<td>Not specified</td>
<td>388</td>
<td>321</td>
<td>83</td>
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<td>47</td>
</tr>
<tr>
<td></td>
<td></td>
<td>189</td>
<td>49</td>
</tr>
</tbody>
</table>
Claudin 18.2 – FAST randomized Ph-II

EOX +/- IMAB362 (Zolbetuximab) – Survival (PFS and OS)

EOX + IMAB362

PFS (based on central imaging assessment) in pts with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells

EOX (84)
EOX + IMAB362 80/800 mg/m² (77)
mPFS 4.8 vs 7.9 months
HR 0.47
P=0.0001

OS in pts with 2+/3+ CLDN18.2 staining in ≥ 40% of tumor cells

EOX (84)
EOX + IMAB362 80/800 mg/m² (77)
mOS 8.4 vs 13.2 months
HR 0.51
P=0.0001


Lordanik F et al. ESMO Asia 2016; #2200
## Claudin 18.2 – FAST randomized Ph-II

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>EOX + IMAB362 (800/600 mg/m²)</th>
<th>EOX</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>No. of patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All patients</td>
<td>77</td>
<td>84</td>
<td>0.51 (0.36-0.73)</td>
</tr>
<tr>
<td>Subsite of Tumor*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Gastroesophageal Junction</td>
<td>13</td>
<td>12</td>
<td>0.68 (0.29-1.59)</td>
</tr>
<tr>
<td>Stomach</td>
<td>62</td>
<td>68</td>
<td>0.51 (0.34-0.76)</td>
</tr>
<tr>
<td><strong>Histopathology</strong></td>
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</tr>
<tr>
<td>Diffuse</td>
<td>35</td>
<td>37</td>
<td>0.40 (0.23-0.75)</td>
</tr>
<tr>
<td>Intestinal</td>
<td>26</td>
<td>27</td>
<td>0.67 (0.36-1.23)</td>
</tr>
<tr>
<td>Mixed</td>
<td>10</td>
<td>11</td>
<td>0.49 (0.17-1.37)</td>
</tr>
<tr>
<td>Other</td>
<td>6</td>
<td>9</td>
<td>0.75 (0.24-2.35)</td>
</tr>
<tr>
<td><strong>Measurable Disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>67</td>
<td>65</td>
<td>0.51 (0.35-0.76)</td>
</tr>
<tr>
<td>No</td>
<td>17</td>
<td>12</td>
<td>0.48 (0.19-1.22)</td>
</tr>
<tr>
<td><strong>CLDN18.2 expression</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2+</td>
<td>25</td>
<td>35</td>
<td>0.40 (0.22-0.75)</td>
</tr>
<tr>
<td>3+</td>
<td>52</td>
<td>49</td>
<td>0.56 (0.36-0.88)</td>
</tr>
<tr>
<td><strong>CLDN18.2 cellular staining</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>rate &lt;70%</td>
<td>20</td>
<td>25</td>
<td><strong>EOX+IMAB better</strong></td>
</tr>
<tr>
<td></td>
<td>57</td>
<td>59</td>
<td><strong>EOX better</strong></td>
</tr>
<tr>
<td>&gt;70%</td>
<td></td>
<td></td>
<td>0.75 (0.40-1.43)</td>
</tr>
<tr>
<td><strong>Previous Gastrectomy</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>56</td>
<td>61</td>
<td>0.40 (0.26-0.62)</td>
</tr>
<tr>
<td>Yes</td>
<td>21</td>
<td>23</td>
<td>0.84 (0.43-1.65)</td>
</tr>
</tbody>
</table>

Lordick F et al. *ESMO Asia 2016; #2200*
SPOTLIGHT: Phase 3, Global, Multi-Center, Double-Blind, Randomized, Efficacy Study of Zolbetuximab (IMAB362) Plus mFOLFOX6 Compared With Placebo Plus mFOLFOX6 as First-line Treatment of Subjects With Claudin (CLDN)18.2-Positive, HER2-Negative, Locally Advanced Unresectable or Metastatic Gastric or Gastroesophageal Junction (GEJ) Adenocarcinoma

- **550 participants**
- 1st line advanced GC
- CLDN18.2 pos in ≥ 75% of tumor cells
- Her2 negative

Loading dose of **zolbetuximab** at Cycle 1 Day 1 followed by a lower dose in subsequent cycles every 3 weeks. Additionally 12 treatments of mFOLFOX6

Placebo starting at Cycle 1 Day 1 and every 3 weeks thereafter. Additionally 12 treatments of mFOLFOX6

Primary endpoint: PFS; secondary: OS, ORR, DOR, HrQoL

Lordick F et al. ESMO Asia 2016; #2200
Anti-Angiogenic Approach

Dr. Judah Folkman, Boston 1933–2008

Folkman’s Hypothesis

http://3quarksdaily.blogs.com/3quarksdaily/images/12folkman_1.jpg

Anti-Aangiogenic 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&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>PFS (med, Mon)</td>
<td>2.1</td>
<td>1.3</td>
<td>HR 0.48</td>
<td>p &lt;0.0001</td>
</tr>
<tr>
<td>OS (med, Mon)</td>
<td>5.2</td>
<td>3.8</td>
<td>HR 0.78</td>
<td>p =0.047</td>
</tr>
</tbody>
</table>

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

Ramucirumab 2nd-line Mono

**Median OS (months) by Study Arm**

- **REGARD: Ramucirumab vs PBO (BSC)**
  - (n=355)
  - Median OS: 5.2 months (Active Treatment), 3.8 months (BSC)

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

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

- **German: Irinotecan vs BSC\(^3\)**
  - (n=40)
  - Median OS: 4.0 months (Active Treatment), 2.4 months (BSC)

---


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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>


© University Cancer Center Leipzig (UCCL): Prof. Dr. Florian Lordick
### Ramucirumab 2nd-line Quality of Life (RAINBOW)

<table>
<thead>
<tr>
<th>Scale</th>
<th>N (RAM+PTX)</th>
<th>N (PBO+PTX)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Global health status</td>
<td>161</td>
<td>136</td>
<td>0.929 (0.734, 1.176)</td>
</tr>
<tr>
<td>Physical functioning</td>
<td>173</td>
<td>148</td>
<td>0.834 (0.663, 1.048)</td>
</tr>
<tr>
<td>Role functioning</td>
<td>190</td>
<td>171</td>
<td>0.868 (0.703, 1.071)</td>
</tr>
<tr>
<td>Emotional functioning</td>
<td>112</td>
<td>117</td>
<td>0.642 (0.491, 0.840)</td>
</tr>
<tr>
<td>Cognitive functioning</td>
<td>150</td>
<td>132</td>
<td>0.803 (0.633, 1.019)</td>
</tr>
<tr>
<td>Social functioning</td>
<td>167</td>
<td>140</td>
<td>0.933 (0.741, 1.175)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>194</td>
<td>174</td>
<td>0.823 (0.666, 1.016)</td>
</tr>
<tr>
<td>Nausea and vomiting</td>
<td>121</td>
<td>121</td>
<td>0.746 (0.574, 0.969)</td>
</tr>
<tr>
<td>Pain</td>
<td>149</td>
<td>137</td>
<td>0.808 (0.636, 1.027)</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>133</td>
<td>110</td>
<td>0.992 (0.766, 1.286)</td>
</tr>
<tr>
<td>Insomnia</td>
<td>118</td>
<td>107</td>
<td>0.807 (0.617, 1.057)</td>
</tr>
<tr>
<td>Appetite loss</td>
<td>133</td>
<td>121</td>
<td>0.813 (0.631, 1.048)</td>
</tr>
<tr>
<td>Constipation</td>
<td>124</td>
<td>93</td>
<td>0.980 (0.743, 1.292)</td>
</tr>
<tr>
<td>Diarrhoea</td>
<td>138</td>
<td>83</td>
<td>1.333 (1.007, 1.764)</td>
</tr>
<tr>
<td>Financial difficulties</td>
<td>102</td>
<td>81</td>
<td>0.973 (0.721, 1.313)</td>
</tr>
</tbody>
</table>

CI, 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+ pacitaxel</th>
<th>Placebo+ pacitaxel</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<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 Group</th>
<th>Placebo Group</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab</td>
<td>64</td>
</tr>
<tr>
<td>Placebo</td>
<td>174</td>
</tr>
</tbody>
</table>

Overall: 238 vs 117

HR (95% CI): 0.871 (0.556-1.366), 0.800 (0.582-1.101), 0.776 (0.603-0.998)

Favours ramucirumab Favours placebo

RAINBOW STUDY

<table>
<thead>
<tr>
<th>Group</th>
<th>Ramucirumab+ Paclitaxel</th>
<th>Placebo+ Paclitaxel</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>330</td>
<td>335</td>
</tr>
<tr>
<td>Peritoneal metastasis</td>
<td>163</td>
<td>152</td>
</tr>
<tr>
<td>No</td>
<td>167</td>
<td>183</td>
</tr>
</tbody>
</table>

HR (95% CI): 0.807 (0.678-0.962), 0.807 (0.627-1.038), 0.758 (0.589-0.976)

Favours ramucirumab Favours placebo


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### Anti-Angiogenic Treatment in Perioperative 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>
</tr>
<tr>
<td>AVATAR</td>
<td>1st-line metastatic</td>
<td>BEV+C</td>
<td>XP</td>
<td>3</td>
</tr>
<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-Fluorouracil, 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

#### Disease setting

<table>
<thead>
<tr>
<th>Localized</th>
<th>Locally advanced</th>
<th>1st</th>
<th>2nd</th>
<th>3rd</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perioperative or Adjuvant</td>
<td>Metastatic and Mostly Palliative</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

- **Localized**
  - Bev: NSABP C-08
  - Bev: AVANT
  - Bev: QUASAR 2

- **Locally advanced**
  - Bev: STO:3
  - Bev: AVAGAST
  - Bev: AVATAR
  - Ram: RAINFALL

- **1st**
  - Ram: RAINBOW
  - Ram: REGARD

- **2nd**
  - Bev: E3200
  - Afli: VELOUR
  - Ram: RAISE

- **3rd**
  - REG: CORRECT, CONCUR

#### Stomach Cancer

- Bev: STO:3
- Bev: AVAGAST
- Bev: AVATAR
- Ram: RAINFALL
- Ram: RAINBOW
- Ram: REGARD
- Apatinib

#### Colorectal Cancer

- Bev: NSABP C-08
- Bev: AVANT
- Bev: QUASAR 2
- Bev: AVF2107g
- Bev: NO16966
- Bev: E3200
- Afli: VELOUR
- Ram: RAISE
- REG: CORRECT, CONCUR

---

Yoon HH, ASCO-GI 2015, substantially modified by Muro K

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**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

**3rd-line chemotherapy (TAS102, irinotecan)**

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 in phase-III, but further research is ongoing
- **Claudin18.2** is a novel promising target for advanced GC treatment. Phase III studies are on the way
- **Ramucirumab** alone and - even more - **ramucirumab plus paclitaxel** improves survival in 2nd-line gastric cancer
Greetings from Leipzig, Germany

New building of the University Cancer Center Leipzig (UCCL)