What is the benefit of drug therapy in advanced gastric cancer – and which drugs shall we use?

Prof. Dr. med. Florian Lordick
Director
University Cancer Center Leipzig, Germany
Treatment goals in advanced gastric cancer

Prolong survival and maintain quality of life

Burden of disease

Burden of treatment
Advanced gastric cancer

- This disease is aggressive and difficult to treat
- Most patients are symptomatic
  - Weight loss
  - Abdominal pain
  - Loss of appetite
  - Nausea
- Survival is <1 year in more than half of patients
- Complete responses to chemotherapy are rare
- Responses are mostly of short duration
What we know…

- Chemotherapy prolongs survival
- Chemotherapy improves symptom control
- Combinations are more active than monotherapy
  

- Elderly (>70 years age) benefit equally
  
  *Trumper M et al. Eur J Cancer 2006; 42(7): 827-834*

**Established standard:**
*Platinum-fluoropyrimidine-combination*
What we know…

- Oxaliplatin can substitute for cisplatin
  

- Oral fluoropyrimidines can substitute for i.v. 5-FU
  
  Ajani JA et al. J Clin Oncol 2010;28(9):1547-1553

- A 3rd drug makes CTx more effective but more toxic
  
## Chemotherapy versus best supportive care

<table>
<thead>
<tr>
<th>Study</th>
<th>Setting</th>
<th>Number of patients</th>
<th>Treatment</th>
<th>Response rate (%)</th>
<th>Median overall survival (months)</th>
<th>Quality of life</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrhönen et al. [13]</td>
<td>1st line</td>
<td>21, 20</td>
<td>FEMTX vs. BSC</td>
<td>29</td>
<td>12.3 vs. 3.1 ((P = 0.0006))</td>
<td>–</td>
</tr>
<tr>
<td>Murad et al. [14]</td>
<td>1st line</td>
<td>30, 10</td>
<td>FAMTX vs. BSC</td>
<td>50</td>
<td>9 vs. 3 ((P = 0.001))</td>
<td>–</td>
</tr>
<tr>
<td>Glimelius et al. [15]</td>
<td>1st line</td>
<td>31, 30</td>
<td>ELF vs. BSC</td>
<td>NR</td>
<td>8 vs. 5 (NS)</td>
<td>In favor of ELF</td>
</tr>
<tr>
<td>Thuss-Patience et al. [16]</td>
<td>2nd line</td>
<td>40</td>
<td>Irinotecan vs. BSC</td>
<td>0 (58 stable disease)</td>
<td>4 vs. 2.4 ((P = 0.0023))</td>
<td>–</td>
</tr>
<tr>
<td>Kang et al. [17]</td>
<td>2nd line</td>
<td>202</td>
<td>Irinotecan or docetaxel vs. BSC</td>
<td>6</td>
<td>5.3 vs. 3.8 ((P = 0.007))</td>
<td>–</td>
</tr>
</tbody>
</table>

*FEMTX* fluorouracil/epidoxorubicin/methotrexate, *FAMTX* fluorouracil/doxorubicin/methotrexate, *ELF* etoposide/leucovorin/fluorouracil, *NR* not reported, *NS* not significant

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Lordick F *et al.* Gastric Cancer 2013 Sep 19 [Epub ahead of print], © 2013 with permission by Springer
Drug combinations

Can oxaliplatin substitute for cisplatin?
Oxaliplatin versus cisplatin

Real-2 study
Platinum comparison

No. at risk
Cisplatin 490 187 41 10
Oxaliplatin 474 198 48 10

Oxaliplatin versus cisplatin

AIO study: FLO versus FLP
Overall population

PFS: $p = 0.077$

OS: $p = 0.506$

Oxaliplatin versus cisplatin

AIO study: FLO versus FLP
Elderly patients (≥65 years)

PFS: p = 0.029
OS: p = n. s.

Drug combinations

Can oral fluoropyrimidines substitute for i.v. 5-FU?
Oral fluoropyridines - capecitabine

Real-2 study
Fluoropyrimidine comparison

No. at risk
Fluorouracil 484 178 37 8
Capecitabine 480 206 52 12

Oral fluoropyridines – S1

Oral DPD-inhibiting fluoropyrimidin, consisting of
Tegafur (FT), Gimeracil (CDHP) und Oteracil-Kalium (Oxo)
in a molar ratio of 1 : 0.4 : 1

Tegafur (FT) + Gimeracil (CDHP) + Oteracil-K (Oxo)
Oral fluoropyridines – S1

Treatment with similar efficacy – FLAGS study

S-1  25 mg/m^2 2x/d d1-21
Cisplatin  75 mg/m^2 d1
q4w

5-FU  1000 mg/m^2 d1-5
Cisplatin  100 mg/m^2 d1
q4w

Primary endpoint: Overall survival (superiority)

N=1053

Ajani JA et al. J Clin Oncol 2010;28(9):1547-1553
## Treatment with less toxicity – FLAGS study

### Toxicity in favour of S-1/cisplatin

<table>
<thead>
<tr>
<th>Toxicity</th>
<th>S-1/cisplatin</th>
<th>5-FU/cisplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia G3/4</td>
<td>18.6%</td>
<td>40.0%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>1.7%</td>
<td>6.9%</td>
</tr>
<tr>
<td>Stomatitis G3/4</td>
<td>1.3%</td>
<td>13.6%</td>
</tr>
<tr>
<td>Diarrhoea G1-4</td>
<td>29.2%</td>
<td>38.4%</td>
</tr>
<tr>
<td>Renal AE G1-4</td>
<td>18.8%</td>
<td>33.5%</td>
</tr>
<tr>
<td>Toxic death</td>
<td>2.5%</td>
<td>4.9%</td>
</tr>
</tbody>
</table>

Drug combinations

What is the role of triplets, and especially docetaxel?
More efficacious treatment – Tax-325 study

Tax-325 study (multinational)

Stage IV
n=445

Randomized study for patients with Stage IV disease.

Primary endpoint: Time to progression (TTP)

Docetaxel 75 mg/m² d1
Cisplatin 75 mg/m² d1
5-FU 750 mg/m² d1-5 q3w

Cisplatin 100 mg/m² d1
5-FU 1000 mg/m² d1-5 q4w

More efficacious treatment – Tax-325 study

Response rate
37% vs. 25%  \( p=0.01 \)

Time to progression
5.6 vs. 3.7 months  \( p \leq 0.01 \)

Survival
9.2 vs. 8.6 months  \( p=0.02 \)

Kaplan-Meier curve: Time to progression

QoL measurements Tax-325 study

Longer preservation of the EORTC Global Health Status with more effective treatment

Toxicity with classical DCF

Haematologic toxicity in DCF

Neutropenia grade 3/4  82%
Febrile neutropenia    30%

Alternative docetaxel-based triplets

**GastroTax-1**

Docetaxel 40 mg/m² + cisplatin 40 mg/m² 2-weekly
5-FU 2000 mg/m² – folinic acid 200 mg/m² weekly

Response rate 46.6%
Time to progression (metastatic) 8.1 months
Survival (metastatic) 15.1 months


**FLOT**

Docetaxel 50 mg/m² + modified FOLFOX 2-weekly

Response rate 53%
Time to progression 5.3 months
Survival 11.3 months

## Alternative docetaxel-based drug combinations

<table>
<thead>
<tr>
<th>Study</th>
<th>Phase</th>
<th>Number of patients</th>
<th>Regimen</th>
<th>Overall response rate (%)</th>
<th>Median PFS (months)</th>
<th>Median OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>van Cutsem et al. [41]</td>
<td>III</td>
<td>224</td>
<td>DCF</td>
<td>37</td>
<td>5.6</td>
<td>9.2</td>
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<tr>
<td>Q3w</td>
<td></td>
<td>221</td>
<td>CF</td>
<td>25</td>
<td>3.7</td>
<td>8.6</td>
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<tr>
<td>Roth et al. [54]</td>
<td>II</td>
<td>61</td>
<td>TCF</td>
<td>41</td>
<td>4.6</td>
<td>10.4</td>
</tr>
<tr>
<td>Q3w</td>
<td></td>
<td>59</td>
<td>TC</td>
<td>38</td>
<td>3.6</td>
<td>11.0</td>
</tr>
<tr>
<td>Tebbutt et al. [44]</td>
<td>II</td>
<td>50</td>
<td>wDCF</td>
<td>47</td>
<td>5.9</td>
<td>11.2</td>
</tr>
<tr>
<td>Q3w</td>
<td></td>
<td>56</td>
<td>wDX</td>
<td>26</td>
<td>4.6</td>
<td>10.1</td>
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<tr>
<td>Shah et al. [69]</td>
<td>II</td>
<td>30</td>
<td>mDCF</td>
<td>52</td>
<td>NR</td>
<td>15.1</td>
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<tr>
<td>Q3w</td>
<td></td>
<td>31</td>
<td>DCF + G-CSF</td>
<td>34</td>
<td>NR</td>
<td>12.6</td>
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<tr>
<td>Van Cutsem et al. [70]</td>
<td>II</td>
<td>79</td>
<td>TE Q3w</td>
<td>23.1</td>
<td>4.5</td>
<td>9.0</td>
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<tr>
<td>Q2w/Q3w</td>
<td></td>
<td>89</td>
<td>TEF Q2w</td>
<td>46.6</td>
<td>7.7</td>
<td>14.6</td>
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<td></td>
<td></td>
<td>86</td>
<td>TEX Q3w</td>
<td>25.6</td>
<td>5.6</td>
<td>11.3</td>
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<tr>
<td>Al-Batran et al. [43]</td>
<td>II</td>
<td>54</td>
<td>FLOT</td>
<td>58</td>
<td>5.2</td>
<td>11.1</td>
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<tr>
<td>Q2w</td>
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<tr>
<td>Lorenzen et al. [42]</td>
<td>II</td>
<td>60</td>
<td>T-PLF</td>
<td>47</td>
<td>8.1</td>
<td>15.1</td>
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<tr>
<td>Q2w</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Yoshida et al. [46]</td>
<td>II</td>
<td>48</td>
<td>DS</td>
<td>56.3</td>
<td>7.3</td>
<td>14.3</td>
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<tr>
<td>Q3w</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Koizumi et al. [48]</td>
<td>II</td>
<td>59</td>
<td>DCS</td>
<td>81</td>
<td>8.7</td>
<td>18.5</td>
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<tr>
<td>Q4w</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yoshida et al. [47]</td>
<td>III</td>
<td>314</td>
<td>DS</td>
<td>38.8</td>
<td>5.3</td>
<td>12.5</td>
</tr>
<tr>
<td>Q3w</td>
<td></td>
<td>314</td>
<td>S</td>
<td>26.8</td>
<td>4.2</td>
<td>10.8</td>
</tr>
</tbody>
</table>

Lordick F et al. Gastric Cancer 2013 Sep 19 [Epub ahead of print], © 2013 with permission by Springer
Docetaxel-based drug combinations

- Docetaxel-triplets can be used in selected patients
- Increased activity and efficacy
- Prolonged maintenance of QoL
- …but at the cost of increased toxicity
Targeted therapy 1st-line

EGFR Family

EGFR: Epidermal Growth Factor Receptor

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

Immunohistochemistry – HER2 protein expression

Her2: 2+

With courtesy of Prof. Donhuijsen, Institute of Pathology Braunschweig
HER2 BDISH – HER2 gene amplification

Amplified

With courtesy of Prof. Donhuijsen, Institute of Pathology Braunschweig
**HER2 screening study - ToGA**

- **3665 samples** from 24 countries (Asia, Europe, Latin America)
- Her2-FISH (pharmDX) and IHC (HercepTest)
- Definition of Her2-positivity: FISH+* and / or IHC 3+

**Results**

- **Her2 positive** 22.1%
  - EG junction vs. stomach 33.2% vs. 20.9%  p<0.001
  - Intestinal type vs. diffuse type 32.2% vs. 6.1%  p<0.001

* FISH+: HER2:CEP17 (centromeric probe 17) ratio ≥ 2
Bang YJ *et al.* Lancet 2010;376(9742):687-697
Anti-HER2 treatment study - ToGA

N=584 Stomach and AEG Stage IV

Primary endpoint: Survival (superiority)

Trastuzumab + cisplatin/5-FU or capecitabin q3w
6 cycles; Trastuzumab until progression

Cisplatin/5-FU or capecitabine q3w
6 cycles

Bang YJ et al. Lancet 2010;376(9742):687-697
Anti-HER2 treatment study - ToGA

<table>
<thead>
<tr>
<th></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 YJ et al. Lancet 2010;376(9742):687-697
Anti-HER2 treatment study - ToGA

Overall survival ITT population

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Anti-HER2 treatment study - ToGA

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Anti-HER2 treatment study - ToGA

Overall survival HER2 IHC 3+ or IHC 2+ and FISH+ population

Reprinted from Bang YJ et al. Lancet 2010;376(9742):687-697. Copyright (2010), with permission from Elsevier
1st-line treatment algorithm: Advanced gastric cancer

Immunohistochemistry Her2

- IHC Score 0/1
- FISH-Test Her2
  - FISH -
    - Platin-fluoropyrimidin- (docetaxel)
  - FISH +
    - Trastuzumab + cisplatin-fluoropyrimidin

IHC Score 2

IHC Score 3

Lordick F et al. Gastric Cancer 2013 Sep 19 [Epub ahead of print]
Ongoing randomised controlled anti-HER2 studies

- Ongoing: **JACOB** study
  Trastuzumab + pertuzumab
  (RCT Stage IV, 1st line)

- Ongoing: **GATSBY** study
  TDM-1
  (RCT Stage IV, 2nd line)

- In preparation: **INNOVATION** study
  Trastuzumab + pertuzumab
  (RCT Stage II-III, neoadjuvant)
1st-line treatment algorithm
Advanced gastric cancer

Don't forget:
Quality-assured molecular diagnostic is key to select patients appropriately for targeted treatment
Further approaches in targeted treatment: Advanced esophago-gastric cancer

**MET/EGFR/HER2 gene amplification**

Anti-EGFR directed therapy
EXPAND Study

RANDOM

Cisplatin  80 mg/m² d1
Capecitabine  1000 mg/m² twice daily; d1-14 q3w

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

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

Anti-EGFR directed therapy

EXPAND Study

## Anti-EGFR directed therapy

**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>

cMET is another promising target in gastric cancer

cMET is another promising target in gastric cancer

cMET-Gene-Amplification

cMET is another promising target in gastric cancer

cMET inhibitor crizotinib: Response after 8 weeks 250 mg/day

cMET is another promising target in gastric cancer

HGF-antibody rilotumumab (AMG102): Randomised Phase II study

**RANDOMISE**

- **Rilotumumab** (15 mg/kg) + ECX Q3W (n = 40)
- **Rilotumumab** (7.5 mg/kg) + ECX Q3W (n = 40)
- **Placebo** + ECX Q3W (n = 40)

**Stratification factors:**
- ECOG PS 0 vs 1
- LA vs. metastatic

**Dosing:**
- E: Epirubicin: 50 mg/m² IV, Day 1
- C: Cisplatin: 60 mg/m² IV, Day 1
- X: Capecitabine: 625 mg/m² BID orally, days 1-21

Courtesy of ESMO. Iveson T *et al.* ESMO/ECCO 2011;abstract
cMET is another promising target in gastric cancer

- Rilotumumab efficacy in patients with cMET high expressing tumours

### Overall survival

<table>
<thead>
<tr>
<th></th>
<th>Median months (80% CI)</th>
<th>HR (80% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms A+B (c-met$^{\text{high}}$, n=27)</td>
<td>11.1 (9.2, 13.3)</td>
<td>0.29 (0.11, 0.76)</td>
</tr>
<tr>
<td>Arm C (c-met$^{\text{high}}$, n=11)</td>
<td>5.7 (4.5, 10.4)</td>
<td></td>
</tr>
</tbody>
</table>

**Patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arms A+B (c-met$^{\text{high}}$)</td>
<td>27  27  26  25  25  24  23  20  19  17  13  12  8  5  2  2  1  0</td>
</tr>
<tr>
<td>Arm C (c-met$^{\text{high}}$)</td>
<td>11  10  10   9   7   4   4   3   3   1   0   0   0   0   0   0   0   0</td>
</tr>
</tbody>
</table>

Courtesy of ESMO. Iveson T et al. ESMO/ECCO 2011;abstract
Ongoing randomised controlled anti-MET studies

- Ongoing: **MetMab** study
  anti-cMET antibody onartuzumab
  (RCT stage IV, 1st line)

- Ongoing: **Rilo Gastric** study
  anti-HGF antibody rilotumumab
  (RCT stage IV, 1st line)
## Second-line chemotherapy of gastric cancer: Randomised studies

<table>
<thead>
<tr>
<th>Study</th>
<th>Protocol</th>
<th>Survival</th>
<th>Symptom control</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2011 Thuss-Patience</strong> (n=40)</td>
<td>Irinotecan vs. BSC</td>
<td>4.0 mon vs. 2.4 mon (p=0.012)</td>
<td>44% improvement vs. 5% improvement</td>
</tr>
<tr>
<td><strong>2012 Kang</strong> (n=202)</td>
<td>Irinotecan or docetaxel vs. BSC</td>
<td>5.3 mon vs. 3.8 mon (p=0.007)</td>
<td>No data</td>
</tr>
<tr>
<td><strong>2013 Cook</strong> (n=168)</td>
<td>Docetaxel vs. BSC</td>
<td>5.2 mon vs. 3.6 mon (p=0.001)</td>
<td>Global QoL unchanged but better symptom control</td>
</tr>
<tr>
<td><strong>2013 Hironaka</strong> (n=219)</td>
<td>Paclitaxel vs. irinotecan</td>
<td>9.5 mon vs. 8.4 mon (p=0.38)</td>
<td>No data</td>
</tr>
</tbody>
</table>
Second-line treatment of gastric cancer

NEWS & VIEWS

GASTROINTESTINAL CANCER

Salvage chemotherapy in gastric cancer—more than a straw?

Florian Lordick

The benefit of salvage chemotherapy in gastric cancer refractory to first-line platinum and fluoropyrimidine therapy was previously unknown. A randomized multicentre study has shown that irinotecan or docetaxel administered as single agents improved survival compared with best supportive care alone. Hence, salvage chemotherapy is now a proven option in pretreated gastric cancer.

Lordick, F. Nat. Rev. Clin. Oncol. 9, 312–313 (2012); published online 1 May 2012; doi:10.1038/nrclinonc.2012.76

Gastric cancer is one of the most common and fatal malignancies. Despite a decreasing incidence in Western civilisations, gastric cancer accounts for approximately 700,000 deaths every year worldwide. Cure can be achieved in the majority of patients. For example, in a Japanese study that compared
Second-line treatment of gastric cancer

Prolong survival and maintain quality of life

Burden of disease

Burden of treatment
Anti-angiogenic treatment

Ramucirumab

Modified from Hicklin DJ and Ellis LM. J Clin Oncol 2005;23(5):1011-1027
Anti-angiogenic treatment 2nd line: REGARD

N=335

Stomach and AEG

Stage IV 2nd-line

119 centres 29 countries

Randomisation 2:1
Primary endpoint: Overall survival (superiority)

Ramucirumab 8 mg/kg q2w until progression

Placebo q2w until progression

Anti-angiogenic treatment 2nd line: REGARD

Median 5.2 versus 3.8 months

# Anti-angiogenic treatment 2nd line: REGARD

<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>
<tr>
<td><strong>Adverse events of special interest</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension§</td>
<td>38 (16%)</td>
<td>18 (8%)</td>
</tr>
<tr>
<td>Bleeding or haemorrhage¶</td>
<td>30 (13%)</td>
<td>8 (3%)</td>
</tr>
<tr>
<td>Arterial thromboembolism¶</td>
<td>4 (2%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Venous thromboembolism**</td>
<td>9 (4%)</td>
<td>3 (1%)</td>
</tr>
<tr>
<td>Proteinuria</td>
<td>7 (3%)</td>
<td>1 (&lt;1%)</td>
</tr>
<tr>
<td>Gastrointestinal perforation</td>
<td>2 (&lt;1%)</td>
<td>2 (&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>0</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>1 (&lt;1%)</td>
<td>0</td>
</tr>
</tbody>
</table>

The RAINBOW trial, a global Phase III study of ramucirumab in combination with paclitaxel in patients with advanced gastric cancer (refractory to or progressive after initial chemotherapy) met its:

- primary endpoint of improved overall survival
- secondary endpoint of improved progression-free survival.
Potential future second-line treatment advanced gastric cancer

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

ECOG PS 0-1 motivation ++
Paclitaxel + Ramucirumab

EGOG 1-2 motivation +/-
Ramucirumab mono

ECOG 3-4 motivation -
ASC (Active Supportive Care)

Lordick F. ESMO Preceptorship Gastric Cancer 2013, Berlin and Singapore
Summary

- Optimal 1st line Tx prolongs survival and can maintain Quality of Life
- Less toxic regimens and drugs should be used
  - e.g. S-1 replaces 5-day i.v. 5-FU
  - e.g. modified DCF regimens when using docetaxel
- Second-line Tx can prolong survival and lead to better symptom control. Anti-angiogenic treatment is a new option
Best Regards from Leipzig
the City of Johann Sebastian Bach