Chemotherapy for Metastatic Disease

Prof. Florian Lordick
University Cancer Center Leipzig
UCCL
- Chemotherapy prolongs survival
- Chemotherapy improves symptom control


- Combinations more effective than 5-FU mono


Established standard: Platinum+Fluoropyrimidine combinations
Metastatic Gastric Cancer 1st line – Standards (II)

- Oxaliplatin can substitute for Cisplatin
  Some advantages, e.g. in elderly patients


- Capecitabine or S-1 can substitute for i.v. 5-FU

  Ajani et al. *J Clin Oncol* 2010; 28: 1547-1553

- A third drug increases the efficacy but also toxicity
  Epirubucine used a lot in UK and NL
  Docetaxel: 3-weekly DCF regimen toxic - modified DCF preferred

  Van Cutsem et al. *J Clin Oncol* 2006; 24: 4991-7
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) - Germany

**Survival**  
Europe / North America: 8-11 months
Platin-based Chemotherapy 1st-line

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Time to progression (months) / PFS</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF</td>
<td>6.2</td>
<td>Cunningham et al. 2006</td>
</tr>
<tr>
<td>DCF</td>
<td>5.6</td>
<td>Van Cutsem et al. 2006</td>
</tr>
<tr>
<td>FOLFOX (mod.)</td>
<td>5.8</td>
<td>Al-Batran et al. 2008</td>
</tr>
<tr>
<td>Cisplatin-S1</td>
<td>6.0</td>
<td>Koizumi et al. 2008</td>
</tr>
<tr>
<td>Cisplatin-Capecitabine</td>
<td>5.6</td>
<td>Kang et al. 2009</td>
</tr>
<tr>
<td>Cisplatin-S1</td>
<td>4.8</td>
<td>Ajani et al. 2010</td>
</tr>
<tr>
<td>Cisplatin-5FU</td>
<td>5.3</td>
<td>Ohtsu et al. 2011</td>
</tr>
<tr>
<td>Cisplatin-Capecitabine</td>
<td>5.6</td>
<td>Lordick et al. 2013</td>
</tr>
<tr>
<td>Irinotecan-5FU-FS</td>
<td>5.7</td>
<td>Guimbaud et al. 2014</td>
</tr>
</tbody>
</table>

Time to progression during 1st-line CTx: 4.8 – 6.2 months
Metastatic Gastric Cancer 1st line – FOLFIRI

Published Ahead of Print on October 6, 2014 as 10.1200/JCO.2013.54.1011
The latest version is at http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2013.54.1011

JOURNAL OF CLINICAL ONCOLOGY
ORIGINAL REPORT

Prospective, Randomized, Multicenter, Phase III Study of Fluorouracil, Leucovorin, and Irinotecan Versus Epirubicin, Cisplatin, and Capecitabine in Advanced Gastric Adenocarcinoma: A French Intergroup (Fédération Francophone de Cancérologie Digestive, Fédération Nationale des Centres de Lutte Contre le Cancer, and Groupe Coopérateur Multidisciplinaire en Oncologie) Study

Rosine Guimbaud, Christophe Lavers, Pauline Bies, Marc Yous, Emile Maillard, Thierry Ayral, Jean-Marc Gormet, Thomas Aparicio, Suzanne Nguyen, Ahmed Azeddine, Pierre-Luc Etienne, Eveline Boucher, Christine Reischach, Pascal Hammel, Philippe Rougier, Laurent Bedenne, and Olivier Bouchet

Abstract

N = 416
FOLFIRI versus ECX first-line

Time to treatment failure in favor of ECX

Overall Survival: 9.5 vs 9.6 mon (p=0.95)

Guimbaud R et al. J Clin Oncol 2014; [epub]
## FOLFIRI 1st-line

<table>
<thead>
<tr>
<th>Schema</th>
<th>Time to progression (Mon)</th>
<th>Survival OS (Mon)</th>
<th>Time to treatment failure (Mon)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI (n=170)</td>
<td>5,0</td>
<td>9,0</td>
<td>4,0</td>
<td></td>
</tr>
<tr>
<td>Cisplatin/5-FU (n=163)</td>
<td>4,2</td>
<td>8,7</td>
<td>3,4</td>
<td></td>
</tr>
<tr>
<td>P-Wert</td>
<td>n.s.</td>
<td>n.s.</td>
<td>0,018</td>
<td>Dank M 2008</td>
</tr>
<tr>
<td>FOLFIRI (n=207)</td>
<td>5,7</td>
<td>9,7</td>
<td>5,1</td>
<td></td>
</tr>
<tr>
<td>ECX (n=209)</td>
<td>5,3</td>
<td>9,5</td>
<td>4,2</td>
<td>Guimbaud R 2014</td>
</tr>
<tr>
<td>P-Wert</td>
<td>n.s.</td>
<td>n.s.</td>
<td>0,008</td>
<td></td>
</tr>
</tbody>
</table>

FOLFIRI 1st-line at least equivalent with Platin-FU-combinations
Question of sequence after neoadjuvant therapy

Which schedule should be used, when a patient already had Platin – FU – perioperatively?

- „Platin-refractory“ – progression during periop. CTx
- „Platin-resistant“ – progression 6-12 mon. after periop. CTx

FOLFIRI is a realistic 1st-line option after periop. platin-based therapy
Maintenance Strategy?

Young Medical Oncologists (YMO)

Georg Martin Haag
Heidelberg
Study PI

Gertraud Stocker
Leipzig
Translational Research

Julia Quidde
Hamburg
QoL Research

Treatment until progression?
De-escalation following induction?
Maintenance strategy?
MATEO study

3 months Induction Polychemo-tx

Investigator’s choice:
mod. Folfox Cisplatin/S-1 FLOT EOX/EOF

Arm A
CR, PR, SD

R
2:1

Arm B
PD

De-escalation: S-1 Maintenance

Continue Polychemo-Tx

CR, PR, SD

Off Study

Primary Endpoint: Overall survival
297 patients will be randomized in 50 centers in Europe.

Correlative research
Who can be managed with S-1 maintenance therapy?
Polymorphisms, Target expression Gene expression profiling
Strategy of Maintenance: AIO-Mateo Study

KEGG annotation of gene signatures

- Focal adhesion
- ECM-receptor interaction
- Cell cycle
- DNA replication
- Various metabolism processes

Sensitive to TKIs?

More sensitive to 5FU?

Lei et al., Gastroenterology 2013; 145: 554-6
## Expression and Drug Sensitivity

<table>
<thead>
<tr>
<th></th>
<th>Mesenchymal</th>
<th>Proliferative</th>
<th>Metabolic</th>
</tr>
</thead>
<tbody>
<tr>
<td>CTx-sensitivity</td>
<td>PI3K-AKT-mTOR inhibitors</td>
<td></td>
<td>5-FU</td>
</tr>
<tr>
<td>in cell lines</td>
<td></td>
<td>-</td>
<td></td>
</tr>
<tr>
<td>Pathway activation</td>
<td>EMT, TGF-B, VEGF, NFKB, mTOR, SHH</td>
<td>E2F, MYC, RAS</td>
<td>SPEM</td>
</tr>
<tr>
<td>Lauren diffuse</td>
<td>58.2%</td>
<td>73.6%</td>
<td>40.6%</td>
</tr>
<tr>
<td>Genetic diffuse</td>
<td>92.5%</td>
<td>28.8%</td>
<td>15.7%</td>
</tr>
<tr>
<td>(Tan et al. 2011)</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

Findings need to be validated in prospective clinical studies

Lei et al., *Gastroenterology* 2013; 145: 554-6
Specific Regimen for Particular Situations?

- High tumor burden / high symptom burden
- Older patients
- Diffuse subtype
High tumor burden / symptoms – Taxane-triplet

Phase III Study of Docetaxel and Cisplatin Plus Fluorouracil Compared With Cisplatin and Fluorouracil As First-Line Therapy for Advanced Gastric Cancer: A Report of the V325 Study Group


Abstract

Docetaxel-CF vs. CF

Response Rate
37% vs. 25% p<0.01

Time to progression
5.6 vs. 3.7 months p<0.01

Survival
9.2 vs. 8.6 months p=0.02

Van Cutsem et al. J Clin Oncol 2006; 24: 4991-7
High tumor burden / symptoms – Taxane-triplett

GastroTax-1 regimen

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

Response rate 46.6%
Time to progression (St. IV) 8.1 months
Survival (St. IV) 15.1 months


FLOT Regime

Docetaxel 50mg/m² + modified FOLFOX 2-weekly

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

Older Patients

FLOT 65+ Study (n=142, median 70 years)

Toxizität Grad 3/4
FLOT: 81.9%
FLO: 38.6% (P < 0.001)

Deterioration on EORTC Global Health scale ≥ 10 points
FLOT: 47.5%
FLO: 20.5% (P < 0.01)

Al-Batran S et al., Eur J Cancer 2013; 49: 2823-2831

FLO: 5-FU-Leucovorin-Oxaliplatin
FLOT: 5-FU-Leucovorin-Oxaliplatin-Docetaxel

PFS
Diffuse Subtype - Molecular Profiles

Genetic heatmaps from 37 cell lines (gene expression)

Validation in patients who received adjuvant 5-FU

G-INT: Genetic Intestinal
G-DIF: Genetic Diffuse

Tan et al. Gastroenterology 2011;141:476-485
Molecular Profiles

Chemosensitivity in cell lines G-INT vs. G-DIF

Figure 4. In vitro chemosensitivity of G-INT and G-DIF cell lines. GI-50 values of 11 G-INT and 17 G-DIF cell lines upon treatment with 5-FU, oxaliplatin, and cisplatin. GI-50 refers to the drug concentration at which 50% growth inhibition is achieved (y-axis: GI-50 enumerated in negative log10). The horizontal gray lines represent the therapeutic concentration patients are exposed to based on pharmacokinetic data. Mean GI-50 concentrations for G-INT and G-DIF cell lines were as follows, respectively: 5-FU, 5.20 μmol/L and 23.22 μmol/L; cisplatin, 38.61 μmol/L and 13.35 μmol/L; oxaliplatin, 1.33 μmol/L and 5.49 μmol/L.

Tan et al. Gastroenterology 2011;141:476-485
**DIGEST Study (ASCO 2015)**

**Primary endpoint: OS**

n=361

<table>
<thead>
<tr>
<th></th>
<th>CS</th>
<th>CF</th>
<th>HR 0.99</th>
</tr>
</thead>
<tbody>
<tr>
<td>Survival</td>
<td>7.5 mon.</td>
<td>6.6 mon.</td>
<td></td>
</tr>
<tr>
<td>Response</td>
<td>34.7%</td>
<td>19.8%</td>
<td>P=0.012</td>
</tr>
<tr>
<td>3° CTC Tox.</td>
<td>45.2%</td>
<td>55.9%</td>
<td></td>
</tr>
</tbody>
</table>

CS does not prolong survival or PFS of patients with diffuse type, metastatic GC compared with CF

Ajani et al. ASCO 2015; abstract 4016
New Molecular Pathways for Diffuse Type

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 (hazard ratio = 0.657; 95% CI 0.485–0.891; one-sided \( P = 0.007 \)). Overall survival benefit for salvage chemotherapy was con-
## 2nd-line Chemotherapy – Randomized Studies

<table>
<thead>
<tr>
<th>Studie</th>
<th>Medikament</th>
<th>Überleben</th>
<th>Verbesserung</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thuss-Patience et al. Eur J Cancer 2011, AIO, D (n=40)</td>
<td><strong>Irinotecan</strong> vs. BSC</td>
<td>4.0 mon vs. 2.4 mon (p=0.012)</td>
<td>HR 0.48 Δ 1.6 months</td>
</tr>
<tr>
<td>Kang et al. J Clin Oncol 2012, Korea (n=202)</td>
<td><strong>Irinotecan</strong> oder <strong>Docetaxel</strong> vs. BSC</td>
<td>5.3 mon vs. 3.8 mon (p=0.007)</td>
<td>HR 0.657 Δ 1.5 months</td>
</tr>
<tr>
<td>Ford et al. Lancet Oncol 2014, COUGAR-02, UK (n=168)</td>
<td><strong>Docetaxel</strong> vs. BSC</td>
<td>5.2 mon vs. 3.6 mon (p=0.001)</td>
<td>HR 0.67 Δ 1.6 months</td>
</tr>
<tr>
<td>Hironaka et al. J Clin Oncol 2013 WJOG, Japan (n=219)</td>
<td><strong>Paclitaxel</strong> vs. <strong>Irinotecan</strong></td>
<td>9.5 mon vs. 8.4 mon (p=0.38)</td>
<td>HR 1.13 Δ 1.1 months</td>
</tr>
</tbody>
</table>
2nd-line Gastric Cancer– Docetaxel - COUGAR

OS 5.3 mon vs. 3.8 mon
HR 0.657 (p=0.007)
△ 1.5 months
RESPONSE 7%

### 2nd-line Gastric Cancer – Docetaxel - COUGAR

#### Events/patients

<table>
<thead>
<tr>
<th>ECOG PS</th>
<th>Docetaxel</th>
<th>ASC</th>
<th>Docetaxel events</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>22/24 (91.7%)</td>
<td>19/22 (86.4%)</td>
<td>-6.0 8.1</td>
<td>0.48 (0.24–0.95)</td>
</tr>
<tr>
<td>1</td>
<td>45/46 (97.8%)</td>
<td>50/50 (100%)</td>
<td>-5.0 22.7</td>
<td>0.80 (0.53–1.21)</td>
</tr>
<tr>
<td>2</td>
<td>13/14 (92.9%)</td>
<td>12/12 (100%)</td>
<td>-1.2 5.9</td>
<td>0.81 (0.36–1.82)</td>
</tr>
<tr>
<td>Stratified</td>
<td>80/84 (95.2%)</td>
<td>81/84 (96.4%)</td>
<td>-12.2 36.7</td>
<td>0.72 (0.52–0.99)</td>
</tr>
</tbody>
</table>

Heterogeneity between groups $\chi^2=1.7$, $p=0.43$

#### Progression

<table>
<thead>
<tr>
<th>Time</th>
<th>Docetaxel</th>
<th>ASC</th>
<th>Docetaxel events</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>During treatment</td>
<td>36/36 (100%)</td>
<td>34/36 (94.4%)</td>
<td>-3.1 16.9</td>
<td>0.83 (0.52–1.34)</td>
</tr>
<tr>
<td>Within 3 months</td>
<td>26/27 (96.3%)</td>
<td>21/22 (95.5%)</td>
<td>-2.6 10.7</td>
<td>0.79 (0.43–1.43)</td>
</tr>
<tr>
<td>3–6 months</td>
<td>18/21 (85.7%)</td>
<td>26/26 (100%)</td>
<td>-9.6 87</td>
<td>0.33 (0.17–0.65)</td>
</tr>
<tr>
<td>Stratified</td>
<td>80/84 (95.2%)</td>
<td>81/84 (96.4%)</td>
<td>-15.3 36.4</td>
<td>0.66 (0.47–0.91)</td>
</tr>
</tbody>
</table>

Heterogeneity between groups $\chi^2=5.3$, $p=0.07$

Unstratified | 80/84 (95.2%) | 81/84 (96.4%) | -15.3 37.6         | 0.67 (0.48–0.92) |

(p=0.01)

### References

2nd-line Gastric Cancer – Docetaxel - COUGAR

Global quality of life
Emotional
Role
Social
Cognitive
Physical
Pain
Fatigue
Constipation
Insomnia
Upset by hair loss
Abdominal pain
Nausea or vomiting
Reflex
Body Image
Dysphagia
Anxiety
Dyspnoea
Dry mouth
Eating
Financial
Appetite loss
Taste
Diarrhoea

Difference in median area under a curve between groups


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Anti-Angiogenic Approach

Ramucirumab 2nd-line (REGARD)

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 Dumitran, Giuseppe Aprile, David RFerry, Bohuslav Melichar, Mustafa Choonal Sivanandan, Joanna Pikiel, Minoru Koshiji, Yan van der Graaf, Trial Investigators*

Summary
Background Vascular endothelial growth factor (VEGF) -mediated angiogenesis can contribute to the pathogenesis of gastric cancer. Several agents targeting VEGF and its receptors have been approved for use in the treatment of gastric cancer. Ramucirumab, a humanised monoclonal antibody against VEGF receptor-2 (VEGFR-2), is approved as first-line salvage therapy for patients with metastatic gastric cancer whose disease has progressed during or after treatment with platinum-based chemotherapy plus fluoropyrimidine.

Ramucirumab was evaluated as part of a global, randomised, placebo-controlled, phase 3 trial in patients with advanced gastric or gastro-oesophageal junction adenocarcinoma who had previously received two or more chemotherapy regimens.

Results Of the 335 patients enrolled, 238 were randomly assigned to ramucirumab and 117 to placebo. The median overall survival time was significantly longer in the ramucirumab group than in the placebo group (3.8 vs 5.2 months; hazard ratio for death 0.776, 95% CI 0.603 to 0.998, p=0.047). The median progression-free survival times were 0.9 months (95% CI 0.6 to 2.1) and 0.5 months (0.3 to 0.9), respectively. The most common grade 3 or 4 adverse events in the ramucirumab group were diarrhoea (25.3%), hypertension (10.4%), and palmar-plantar erythrodysesthesia syndrome (13.9%). The most common adverse events in the placebo group were diarrhoea (27.3%) and hypertension (6.9%).

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

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

Median: 3.8 vs. 5.2 months
Ramucirumab 2nd-line (RAINBOW)

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

1:1
Primary endpoint: survival

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

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><strong>Response Rate</strong></td>
<td>28%</td>
<td>16%</td>
<td>p = 0.0001</td>
</tr>
<tr>
<td><strong>PFS (med, Mon)</strong></td>
<td>4.4 22%</td>
<td>2.9 10%</td>
<td>HR 0.635 p &lt; 0.0001</td>
</tr>
<tr>
<td>6 months (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>OS (med, Mon)</strong></td>
<td>9.6 40%</td>
<td>7.3 30%</td>
<td>HR 0.807 p = 0.0169</td>
</tr>
<tr>
<td>6 months</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Wilke et al., *Lancet Oncol* 2014; [published online 18 September]
2nd-line Therapy of Gastric Cancer

Evaluation of ECOG-Performance Status, tolerability of 1st-line CTx, patient preference, need for remission

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

- **EGOG 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
Warm regards from Leipzig, Germany!