Chemotherapy for metastatic disease

Priv. Doz. Dr. Dr. med. T.O. Götze
Institute of Clinical Cancer Research
Director: Prof. Dr. S.-E. Al- Batran
University Cancer Center Frankfurt
Chemotherapy for metastatic Gastric cancer

• First-line chemotherapy: what`s “standard” and what`s best?
• Second-line chemotherapy: where do we stand?
metastatic disease

• poor prognosis
  – 2-Year survival 10-20%
  – median survival <1 year
• Chemotherapy prolongation of survival (4-11 months)
• Preservation / improvement of QoL
First-line chemotherapy: general data

- offers survival benefit over BSC\(^1\) \(\rightarrow\) HR 0.37 [0.24, 0.55]
- improvement symptom control\(^1\)

- Combination better than single-agent 5-FU\(^1\)
  - Higher RR: OR 2.91 [2.15, 3.93]
  - Prolonged TTP and OS: HR 0.82 [0.74, 0.90]

- Question: is there an optimal combination?

\(^1\)Wagner AD et al. Cochrane Database Syst Rev 2010
First-line chemotherapy: active agents

- Fluoropyrimidines
  - 5-FU
  - Capecitabine
  - S-1

- Platinum derivatives
  - Cisplatin
  - Oxaliplatin

- Camptothecines
  - Irinotecan

- Taxanes
  - Docetaxel

- Other agents
  - Epirubicin
  - MTX
  - Etoposide
  - ...
First-line chemotherapy: active agents

Fluoropyrimidines
- 5-FU
- Capecitabine
- S-1

Camptothecines
- Irinotecan

Platinum derivatives
- Cisplatin
- Oxaliplatin

Taxanes
- Docetaxel

Other agents
- Epirubicin
- MTX
- Etoposide
- ...

• Other agents
First-line chemotherapy: what is the standard/ best regimen?

• Platinum + fluoropyrimidine accepted as an international “standard”
  ✓ OS benefit for platinum vs. non-platinum containing regimen

• Oxaliplatin and cisplatin equally effective
  ✓ different side effects

• Oral fluoropyrimidines (capecitabine / S-1)
  equally effective than intravenous 5-FU

1Wagner AD et al. Cochrane Database Syst Rev 2010;
4Yamada Y et al. Ann Oncol 2014;
6Ajani JA et al. J Clin Oncol 2010
Oral vs. i.v. 5-FU and cis- vs. oxaliplatin

ECF(X): Epirubicin 50 mg/m², d1; cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or capecitabine 1250 mg/m² p.o. divided into two doses d1-d21), every three weeks

CONCLUSIONS
Capecitabine and oxaliplatin are as effective as fluorouracil and cisplatin, respectively, in patients with previously untreated esophagogastric cancer. (Current Controlled
Oral vs. i.v. 5-FU and cis- vs. oxaliplatin

**Conclusion** FLO reduced toxicity as compared with FLP. In older adult patients, FLO also seemed to be associated with improved efficacy.
Oral vs. i.v. 5-FU and cis- vs. oxaliplatin

**Original Article**

*Capecitabine/cisplatin versus 5-fluorouracil/cisplatin as first-line therapy in patients with advanced gastric cancer: a randomised phase III noninferiority trial*


**Conclusions:** XP showed significant noninferiority for PFS versus FP in the first-line treatment of AGC. XP can be considered an effective alternative to FP.
First-line chemotherapy: third-drug for triplet regimen

- Anthracycline = epirubicin, common but still sustainable?

- Initial OS benefit for anthra vs. non-anthra\(^1\) was not confirmed in metaanalysis of Mohammad NH et al\(^2\) 2015

- In a randomized trial by Yun J et al. 2010 [cisplatin/capecitabine (CX) vs. epirubicin plus CX (ECX)] there was no benefit due to adding E to CX\(^3\)

\(^1\)Wagner AD et al. Cochrane Database Syst Rev 2010; 
\(^2\)Mohammad NH et al. Cancer Metastasis Rev 2015; 
\(^3\)Yun J et al. Eur J Cancer 2010;
First-line chemotherapy: active agents

**Fluoropyrimidines**
- 5-FU
- Capecitabine
- S-1

**Platinum derivatives**
- Cisplatin
- Oxaliplatin

**Camptothecines**
- Irinotecan

**Taxanes**
- Docetaxel

**Other agents**
- Epirubicin
- MTX
- Etoposide
- ...
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

Eric Van Cutsem, Vladimir M. Moiseyenko, Sergei Tjulandin, Alejandro Majlis, Manuel Consienla, Corrado Bonti, Adriano Rodrigues, Miguel Fodor, Yee Chao, Edouard Voznyi, Marie-Laure Risse, and Jaffer A. Ajani

<table>
<thead>
<tr>
<th>Grade 3/4 Toxicity</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia</td>
<td>82%</td>
</tr>
<tr>
<td>Febrile Neutropenia</td>
<td>29%</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>21%</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>19%</td>
</tr>
<tr>
<td>Lethargy</td>
<td>19%</td>
</tr>
</tbody>
</table>
First-line chemotherapy: third-drug for triplet regimen

- **Docetaxel increases efficacy**
  - Significantly increased
  - **RR** (37% vs. 25%),
  - **TTP** (5.6 vs. 3.7 months)
  - **OS** (9.2 vs. 8.6 months)
  - but **adds toxicity** (V325 phase III trial \(^1\): DCF vs. CF)
  - Higher grade 3-4 toxicity: neutropenia 82% vs. 57% (Complicated neutropenia/febrile: 29% vs. 12%)

\(^1\)Van Cutsem E et al. J Clin Oncol 2006
First-line chemotherapy: third-drug for triplet regimen

- Bi- rather than three- weekly = mDCF- modified DCF schedules are preferable

- **mDCF**\(^1\): (5-FU 2,000 mg/m\(^2\) intravenously [IV] over 48 hours, docetaxel 40 mg/m\(^2\) IV on day 1, cisplatin 40 mg/m\(^2\) IV on day 3, every **2 weeks**)

- **GastroTax – 1 Regime**\(^2\)(T-PLF): Docetaxel 40mg/m\(^2\) + cisplatin 40mg/m\(^2\) **2-weekly**
  5-FU 2000mg/m\(^2\) – folinic acid 200mg/m\(^2\) weekly

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Biweekly fluorouracil, leucovorin, oxaliplatin, and docetaxel (FLOT) for patients with metastatic adenocarcinoma of the stomach or esophagogastric junction: a phase II trial of the Arbeitsgemeinschaft Internistische Onkologie

S.-E. Al-Batran¹, J. T. Hartmann², R. Hofheinz³, N. Homann⁴, V. Rethwisch⁵, S. Probst⁶, J. Stoehlmacher⁷, M. R. Clemens⁸, R. Mahlberg⁸, M. Fritz⁹, G. Seipelt¹⁰, M. Sievert¹¹, C. Pauligk¹, A. Atmaca¹ & E. Jäger¹

- Taxotere 50 mg/m² d1
- Oxaliplatin 85 mg/m² d1
- Leucovorin 200 mg/m² d1
- FU 2.6 g/m² 24h CI d1
- q2w

- Response rate 58% (FLO 34%)
- Med. survival 11.1 Mo
- Febrile Neutropenia 3.8%
First-line chemotherapy: third-drug for triplet regimen

- **Oxaliplatin** is a appropriate in triplet regimen with 5-FU/Docetaxel

- **FLOT**: oxaliplatin 85 mg/m², leucovorin 200 mg/m² and fluorouracil 2600 mg/m² as a 24-h infusion in combination with docetaxel 50 mg/m² on day 1 every 2 weeks

- **TEF**: docetaxel 50 mg/m² on D1 + oxaliplatin 85 mg/m² on D1 + 5-fluorouracil 2400 mg/m²CIV 46h/ folinic acid 400mg/m² on D1 q2w

2 Van Cutsem E et al., Ann Oncol. 2015
meta-analysis by Mohammad NH et al.

„ triplet versus doublet chemotherapy „
meta-analysis by Mohammad NH et al.

„triplet versus doublet chemotherapy“

- 5-Fu better than without
meta-analysis by Mohammad NH et al.

„triplet versus doublet chemotherapy“

- No benefit for Mito C
meta-analysis by Mohammad NH et al.

„triplet versus doublet chemotherapy“

- No benefit for Epirubicin
meta-analysis by Mohammad NH et al.

„triplet versus doublet chemotherapy“

- Cisplatin based regimen better than non-cisplatin
meta-analysis by Mohammad NH et al.

„triplet versus doublet chemotherapy“

- Taxan based better than non-taxan
meta-analysis by Mohammad NH et al.

„ triplet versus doublet chemotherapy “

- 21 studies with a total of 3475 participants

improvement in
- **overall survival (OS)** (hazard ratio (HR) 0.90, 95% (CI) 0.83-0.97)
- **progression-free survival (PFS)** (HR 0.80, 95% CI 0.69-0.93)
- **better objective response rate (ORR)** (risk ratio 1.25, 95% CI 1.09-1.44)
- risks of grade 3-4 thrombocytopenia (6.2 vs 3.8%), infection (10.2 vs 6.4%), and mucositis (9.7 vs 4.7%) significantly increased

first-line triplet therapy is superior to doublet therapy
# First-line irinotecan + 5-FU

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No.</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
<th>TTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan + 5-FU</td>
<td>170</td>
<td>31.8%</td>
<td>5.0</td>
<td>9.0</td>
<td>4.0</td>
</tr>
<tr>
<td>Cis + 5-FU</td>
<td>163</td>
<td>25.8%</td>
<td>4.2</td>
<td>8.7</td>
<td>3.4</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>0.23</td>
<td>0.088</td>
<td></td>
<td>0.018</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No.</th>
<th>Overall</th>
<th>Neutropenia (febrile neutropenia)</th>
<th>Diarrhea</th>
<th>Tox death</th>
</tr>
</thead>
<tbody>
<tr>
<td>Irinotecan + 5-FU</td>
<td>170</td>
<td>NR</td>
<td>24.8% (4.8%)</td>
<td>21.6%</td>
<td>1</td>
</tr>
<tr>
<td>Cis + 5-FU</td>
<td>163</td>
<td>NR</td>
<td>51.6% (10.2%)</td>
<td>7.2%</td>
<td>5</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>NR</td>
<td></td>
</tr>
</tbody>
</table>

- IF did not yield a significant TTF or OS superiority over CF
- IF is a platinum-free regimen that has similar efficacy to CF
- but with improved tolerance

FOLFIRI vs. ECX in Firstline

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 Francophone de Cancérologie Digestive).

Table 2. Efficacy Results for PFS and OS

<table>
<thead>
<tr>
<th>Variable</th>
<th>ECX Arm (n = 209)</th>
<th>FOLFIRI Arm (n = 207)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>95% CI</td>
</tr>
<tr>
<td>PFS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>5.29</td>
<td>5.03</td>
<td>2.46 to 8.97</td>
</tr>
<tr>
<td>Range</td>
<td>4.53-6.31</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24-month survival</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>OS, months</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median</td>
<td>9.49</td>
<td>11.17</td>
<td>7.03 to 16.36</td>
</tr>
<tr>
<td>Range</td>
<td>8.77-11.14</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: ECX, epirubicin, cisplatin, and capecitabine; FOLFIRI, fluorouracil, leucovorin, and irinotecan; OS, overall survival; PFS, progression-free survival. *Log-rank test.

Guimbaud et al. JCO 2014
# First-line irinotecan + 5-FU

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No.</th>
<th>RR</th>
<th>PFS</th>
<th>OS</th>
<th>TTF</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI</td>
<td>207</td>
<td>37.8%</td>
<td>5.8</td>
<td>9.7</td>
<td>5.1</td>
</tr>
<tr>
<td>ECX</td>
<td>209</td>
<td>39.2%</td>
<td>5.3</td>
<td>9.5</td>
<td>4.2</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>NS</td>
<td>0.96</td>
<td>HR=1.01</td>
<td>0.008</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Regimen</th>
<th>No.</th>
<th>Overall</th>
<th>Hematologic</th>
<th>Non-hematologic</th>
<th>Tox death</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOLFIRI</td>
<td>207</td>
<td>69%</td>
<td>38.4%</td>
<td>53.2%</td>
<td>7</td>
</tr>
<tr>
<td>ECX</td>
<td>209</td>
<td>83.5%</td>
<td>64.5%</td>
<td>53.5%</td>
<td>5</td>
</tr>
<tr>
<td>P-value</td>
<td></td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>0.81</td>
<td>NR</td>
</tr>
</tbody>
</table>

- FOLFIRI as first-line treatment significantly better TTF than ECX
- not original ECX- Regimen from REAL-2-study
- no difference in PFS and OS

Guimbaud R et al. J Clin Oncol 2014
First-line chemotherapy: FOLFIRI

FOLFIRI a “standard” first-line option?
- comparable activity and efficacy compared to CF and ECX
- lower hematologic toxicity compared to CF and ECX

Not a new standard but an alternative to a platinum based regimen
Doublet vs. triplet: criteria/open questions

1. age of patient
2. fixed treatment period or until PD?
3. Patient’s condition as a prognostic factor
4. intestinal vs. diffuse type
1.) elderly patients

- **doublet preferable over triplet in fit elderly patients**
  - **FLOT vs. FLO**: no increase in efficacy over 70 years, at the price of increased toxicity and QoL deterioration
  - **V325**: phase III trial: DCF vs. CF

- **Doublet vs. monotherapy**
  - **capecitabine vs. XELOX**: RR 31% vs. 42%, median PFS 3.1 vs. 7.1 months, median OS 5.4 vs. 13.5 months
  - XELOX combination chemotherapy results in improved efficacy
  - does not increase toxicities in elderly patients with AGC
  - DSMB stopped trial based on the evidence of superiority with XELOX
  - In vulnerable elderly patients, single-agent fluoropyrimidine can be considered
  - When doublets are administered, early stop (after 3-4 months) may be reasonable
  - fluoropyrimidine maintenance an option

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3. Hwang IG et al. ASCO Ann Meeting 2015 (abstr. 4051)
2.) fixed treatment period or until PD?

- in randomized trials Chemotherapy generally scheduled until PD
  - risk of cumulative toxicity
  - PFS rarely exceeding 6 months in first-line trials
- Optimal treatment duration unknown → trials ongoing (e.g. RAINFALL/MATEO)
- De-escalation (e.g. fluoropyrimidine maintenance) or treatment holidays after 6 months can be considered
Discontinuation of first-line chemotherapy (CT) after 6 weeks of CT in patients with metastatic squamous-cell esophageal cancer: A randomized phase II trial.

Adenis A¹, Bennouna J², Etienne PL³, Bogart E¹, Francois E⁴, Galais MP⁵, Ben Abdelghani M⁶, Kotecki N¹, Michel P⁷, Metges JP⁸, Dahan L⁹, Piessen G¹⁰, Conroy T¹¹, Ghiringhelli F¹², Bedenne L¹³, El Hajbi F¹, Samalin E¹⁴, Clisant S¹, Penel N¹, Mariette C¹⁰.

¹Centre Oscar Lambret (Lille); ²Institut de Cancérologie de l’Ouest (Nantes); ³CARIO-HPCA (Plérin); ⁴Centre Lacassagne (Nice); ⁵Centre Baclesse (Caen); ⁶Centre P.Strauss (Strasbourg); ⁷University Hospital (Rouen); ⁸University Hospital (Brest); ⁹University Hospital (Marseille); ¹⁰University Hospital (Lille); ¹¹Institut de Cancérologie de Lorraine (Nancy); ¹²Centre GF.Leclerc (Dijon); ¹³University Hospital (Dijon); ¹⁴Institut de Cancérologie (Montpellier), France
Background

Metastatic esophageal cancer

• In metastatic esogastric adenocarcinoma, palliative chemo prolongs survival, and improves quality of life

• In metastatic squamous cell esophageal cancer (MSEC)
  – there is no available evidence supporting a survival benefit with chemo for such patients, because randomized trials such as “CT vs BSC” are lacking.
  – tumor responses have been documented with fluoropyrimidins, platinum compounds, taxanes, and with vinorelbine.
The E-DIS trial

We designed a chemo-discontinuation randomized phase 2 trial, in patients free from progression after 6 weeks of a 5FU/platinum-based CT.

Main eligibility criteria (selection part)
- Histologically-proven MSEC
- Measurable/Evaluable disease, ECOG- PS≤2
- Previously untreated for metastatic disease

Eligibility criteria (randomized part)
- Non progressive disease at W6, & PS≤2

Eligible patients for SELECTION PART
Fluoropyrimidin/platinum-based chemo (CT)

Tumor assessment at 6wks ± 7d

Non progressive disease (and PS≤2)

Progressive disease

End of study

CT CONTinuation + BSC
CT DIScontinuation + BSC

In case of PD or intolerance, treatment is left at physician’s choice

Stratification factors
- Previous chemo (or not) in the neoadj/adj setting
- Dysphagia: Atkinson 1-2 vs 3-4
- EQ-5D visual analog scale <40/≥40

Presented by: Prof. Antoine ADENIS
Results

Flow Chart

Selection part

- Selection n=105
- Ineligible (2)
  - Not treated (patient decision) (1)

Randomized part

- Eligible & treated n=31
  - Per-protocol analysis
- Eligible & treated n=33
- Chemo CONT n=34
  - ITT analysis
- Chemo DIScont n=33

1:1 Randomization

- Non progressive & ECOG PS 0-1-2 n=67

Evaluable for tumor assessment n=90
Conclusion. 2

- At this point, we consider that either chemo CONT + BSC or chemo DIScont + BSC are both adequate standard treatments (physician & patient choice) for further randomized trial in that setting.

Is it really possible that 6 weeks of FOLFOX are as good as FOLFOX until progression?
Conclusion. 2 (modified)

- At this point, we consider that either chemo CONT + BSC or chemo DIScont + BSC + chemo on progression are both adequate standard treatments: Perhaps an OPTIMOX 2* STOP and GO approach would not be so bad?

*Chibaudel, J Clin Oncol 2009
**Conclusion. 2**

- Although **chemo until progression** or **stop and go chemo** may offer similar overall survival.
- Median QOL “appears” >50% better on chemo than without.
- Based on these limited data, I would still choose **FOLFOX until POD**.
3.) Clinical prognostic factors

- Among 1080 UK patients treated with 5-FU-based regimens, the following factors resulted associated with worse OS:
  - ECOG performance status ≥2
  - liver involvement
  - peritoneal involvement
  - alkaline phosphatase ≥100 U/L

Good risk: no risk factors
Moderate risk: 1-2 risk factors
Poor risk: 3-4 risk factors

Chau I et al. J Clin Oncol 2004
Clinical prognostic factors

• Among 1445 Asian patients treated with different first-line regimens, the factors associated with worse OS:

- ECOG performance status ≥2
- bone metastases
- no prior gastrectomy
- ascites
- alkaline phosphatase >85 U/L
- albumin <3.6 g/dL

Good risk: 0-1 risk factors
Moderate risk: 2-4 risk factors
Poor risk: 5-6 risk factors

4.) Lauren classification and path. remission: FLOT vs. ECF/ECX

<table>
<thead>
<tr>
<th>Regimen</th>
<th>Intestinal (n)</th>
<th>Mixed (n)</th>
<th>Diffuse (n)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>16% (112)</td>
<td>6% (18)</td>
<td>3% (73)</td>
</tr>
<tr>
<td>FLOT</td>
<td>23% (52)</td>
<td>0% (11)</td>
<td>3% (34)</td>
</tr>
<tr>
<td>ECF/ ECX</td>
<td>10% (60)</td>
<td>14% (7)</td>
<td>3% (39)</td>
</tr>
</tbody>
</table>

Rates of ypCR according to Lauren’s histological subtypes

Al- Batran et al. Lancet Oncol in press
Complete and subtotal pathological remission according to subtype of Lauren

Untreated metastatic diffuse gastric adenocarcinoma (DGAC): the DIGEST trial
Randomized phase III study of S-1 and cisplatin vs. 5-FU and cisplatin

- prognosis for metastatic DGAC is poor
- but first line therapy for DGAC is the same
- analyses of the FLAGS study suggested
  - S-1/Cisplatin might be better than 5-FU/cisplatin in DGAC

The trial did **not** reach its primary endpoint (OS)
- no difference in OS: 7.5 vs. 6.6 months (HR=0.99, p=0.931)
- no difference in PFS
- higher RR with CS: 34.7% vs. 19.8% (p=0.012)

Ajani JA et al. ASCO Annual Meeting 2015
## Second-line chemotherapy: overview

<table>
<thead>
<tr>
<th>Year</th>
<th>Journal</th>
<th>Authors</th>
<th>Trial/regimen</th>
<th>OS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>2011</td>
<td>Eur J Cancer</td>
<td>Thuss-Patience et al.</td>
<td>Irinotecan vs. BSC AIO (n=40)</td>
<td>4.0 vs. 2.4 months (p=0.012)</td>
</tr>
<tr>
<td>2012</td>
<td>J Clin Oncol</td>
<td>Kang et al.</td>
<td>Irinotecan or Docetaxel vs. BSC (n=202)</td>
<td>5.3 vs. 3.8 months (p=0.007)</td>
</tr>
<tr>
<td>2014</td>
<td>Lancet Oncol</td>
<td>Ford HE et al.</td>
<td>Docetaxel vs. BSC Cougar-02 (n=168)</td>
<td>5.2 vs. 3.6 months (p=0.01)</td>
</tr>
<tr>
<td>2014</td>
<td>Lancet</td>
<td>Fuchs CS et al.</td>
<td>Ramucirumab vs. BSC REGARD (n=348)</td>
<td>5.2 vs. 3.8 months (p=0.0473)</td>
</tr>
<tr>
<td>2014</td>
<td>Lancet Oncol</td>
<td>Wilke H et al.</td>
<td>Paclitaxel+ Ramucirumab/Placebo RAINBOW (n=665)</td>
<td>9.63 vs. 7.36 months (p=0.0169)</td>
</tr>
<tr>
<td>2013</td>
<td>J Clin Oncol</td>
<td>Hironaka S et al.</td>
<td>Paclitaxel vs. Irinotecan (n=219)</td>
<td>9.5 vs. 8.4 months (p=0.38)</td>
</tr>
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</table>
Irinotecan und Taxane beim vorbehandelten metastasierten Magenkarzinom wirksam

Docetaxel 60 mg/m² qw3 oder irinotecan 150 mg/m² qw2 (Park et al JCO 2012)

Docetaxel 75 mg/m² qw3 (Ford et al 2013)

Irinotecan 250 mg/m² q3w (Thuss-Patience et al EJC 2011)
VEGFR - Ramucirumab: Second-line chemotherapy

REGARD RAINBOW

P=0.047
3.8 vs. 5.2 Monate

P=0.017
7.4 vs. 9.6 Monate

Fuchs et al. Lancet 2013
Wilke et al. Lancet Oncol 2014
VEGF/R?
### VEGF/R: 2nd - 3rd - Line

<table>
<thead>
<tr>
<th>Line</th>
<th>Trial</th>
<th>N</th>
<th>Treatment</th>
<th>1st Endpt</th>
<th>mOS</th>
<th>HR</th>
<th>Δ</th>
<th>mPFS</th>
<th>HR</th>
<th>Δ</th>
<th>RR</th>
<th>Δ</th>
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<tbody>
<tr>
<td>2L</td>
<td>Fuchs et al, Lancet 2013 Regard</td>
<td>335</td>
<td>Placebo Ramucirumab</td>
<td>OS</td>
<td>3.5</td>
<td>5.2</td>
<td>+1.7</td>
<td>1.3</td>
<td>2.1</td>
<td>0.48</td>
<td>+0.8</td>
<td>3%</td>
</tr>
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<td></td>
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<td>Placebo Ramucirumab</td>
<td>OS</td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>2L</td>
<td>Wilke et al, Lancet Oncol 2014 RAINBOW</td>
<td>665</td>
<td>Paclitaxel-Plbo Paclitaxel-Ram</td>
<td>OS</td>
<td>7.4</td>
<td>9.6</td>
<td>+2.2</td>
<td>2.9</td>
<td>4.4</td>
<td>0.64</td>
<td>+1.5</td>
<td>16%</td>
</tr>
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<td></td>
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<td>Paclitaxel-Plbo Paclitaxel-Ram</td>
<td>OS</td>
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<tr>
<td>3L</td>
<td>Li et al, J Clin Oncol 2016 in press</td>
<td>267</td>
<td>Placebo Apatinib</td>
<td>OS/PFS</td>
<td>4.7</td>
<td>6.5</td>
<td></td>
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</tr>
</tbody>
</table>

#### Primary lesion
- Gastric
- Gastro-oesophageal junction
- Unknown

#### Location of primary tumour (%)
- Gastric: 17/8 (75%) 87 (74%)
- Gastro-oesophageal junction: 20/25 (25%) 30 (26%)

#### Histological subtype (%)
- Intestinal: 52 (22%) 35 (30%)
- Diffuse: 96 (40%) 44 (38%)
- Unknown or NA: 90 (38%) 38 (32%)

#### Site of primary tumour
- Gastric: 264 (80%) 264 (79%)
- Gastro-oesophageal junction: 66 (20%) 71 (21%)
# VEGF/R: 1st-Line

<table>
<thead>
<tr>
<th>Line</th>
<th>Trial</th>
<th>N</th>
<th>Treatment</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Endpt</th>
<th>mOS</th>
<th>HR</th>
<th>Δ</th>
<th>mPFS</th>
<th>HR</th>
<th>Δ</th>
<th>RR</th>
<th>Δ</th>
</tr>
</thead>
<tbody>
<tr>
<td>1&lt;sup&gt;L&lt;/sup&gt;</td>
<td>Ohtsu et al</td>
<td>774</td>
<td>Cis/F-placebo Cis/F-Bev</td>
<td>OS</td>
<td>10.1</td>
<td>12.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;L&lt;/sup&gt;</td>
<td>Shen et al</td>
<td>202</td>
<td>Cis/Cape-placebo Cis/Cape-Bev</td>
<td>OS</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>1&lt;sup&gt;L&lt;/sup&gt;</td>
<td>Yoon et al</td>
<td>168</td>
<td>FOLFOX-placebo FOLFOX-Ram</td>
<td>PFS</td>
<td>11.7</td>
<td>11.5</td>
<td></td>
<td>6.7</td>
<td>6.4</td>
<td></td>
<td>46</td>
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<tr>
<td>1&lt;sup&gt;L&lt;/sup&gt;</td>
<td>Enzinger et al</td>
<td>64</td>
<td>FOLFOX-placebo FOLFOX-Afliber</td>
<td>6m PFS 57.1% 60.5% N.S.</td>
<td>18.7</td>
<td>13.7</td>
<td></td>
<td>7.3</td>
<td>9.9</td>
<td></td>
<td>75</td>
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sectable, locally advanced or metastatic adenocarcinoma of the stomach or gastroesophageal junction were assigned to bevacizumab (n = 387) or placebo (N.S. p<0.004 p<0.03)
### HER 2 +: 1st vs. 2nd

<table>
<thead>
<tr>
<th>Line</th>
<th>Trial</th>
<th>N</th>
<th>Treatment</th>
<th>1&lt;sup&gt;st&lt;/sup&gt; Endpt</th>
<th>mOS</th>
<th>HR</th>
<th>Δ mOS</th>
<th>HR</th>
<th>Δ HR</th>
<th>RR</th>
<th>Δ RR</th>
<th>Δ RR</th>
</tr>
</thead>
<tbody>
<tr>
<td>1L</td>
<td>1. Bang et al&lt;br&gt;Lancet 2010&lt;br&gt;TOGA</td>
<td>584</td>
<td>Cis/FP&lt;br&gt;Cis/FP – tras</td>
<td>OS</td>
<td>11.8&lt;sup&gt;<em>&lt;/sup&gt;&lt;br&gt;16&lt;sup&gt;</em>&lt;/sup&gt;</td>
<td>0.74&lt;br&gt;0.65&lt;sup&gt;*&lt;/sup&gt;&lt;br&gt;P&lt;0.05</td>
<td>+2.7&lt;br&gt;+4.2&lt;sup&gt;*&lt;/sup&gt;&lt;br&gt;P&lt;0.01</td>
<td>5.5&lt;br&gt;6.7</td>
<td>0.71&lt;br&gt;0.72&lt;br&gt;P&lt;0.001</td>
<td>+1.2&lt;br&gt;+1.8&lt;br&gt;P&lt;0.03</td>
<td>35%&lt;br&gt;47%&lt;br&gt;72%</td>
<td>+12&lt;br&gt;+18&lt;br&gt; +20</td>
</tr>
<tr>
<td>1L</td>
<td>2. Hecht et al&lt;br&gt;J Clin Oncol 2015&lt;br&gt;LOGIC</td>
<td>545&lt;br&gt;(487)</td>
<td>Cis/FP&lt;br&gt;Cis/FP - lapat</td>
<td>OS</td>
<td>10.5&lt;br&gt;12.2</td>
<td>0.91&lt;br&gt;0.82&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>+1.7&lt;br&gt;6</td>
<td>5.4&lt;br&gt;6</td>
<td>0.82&lt;br&gt;0.86&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>+0.6&lt;br&gt;+0.6&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>39%&lt;br&gt;53%&lt;br&gt;72%</td>
<td>+14&lt;br&gt;+18&lt;br&gt; +20</td>
</tr>
<tr>
<td>2L</td>
<td>3. Satoh et al&lt;br&gt;J Clin Oncol 2014&lt;br&gt;TYTAN</td>
<td>261</td>
<td>Paclitaxel&lt;br&gt;Paclitaxel-lapat</td>
<td>OS</td>
<td>8.9&lt;br&gt;11</td>
<td>0.84&lt;br&gt;0.84&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>+2.1&lt;br&gt;5.5</td>
<td>4.4&lt;br&gt;5.5</td>
<td>0.84&lt;br&gt;0.84&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>+1.1&lt;br&gt;+1.8&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>9%&lt;br&gt;27%&lt;br&gt;72%</td>
<td>+14&lt;br&gt;+18&lt;br&gt; +20</td>
</tr>
<tr>
<td>2L</td>
<td>4. Kang et al&lt;br&gt;GI ASCO 2016&lt;br&gt;Abstr 5 GATSBY</td>
<td>345&lt;br&gt;(1:2)</td>
<td>Pac38%, D62%&lt;br&gt;T-DM1</td>
<td>OS</td>
<td>8.6&lt;br&gt;7.9</td>
<td>1.15&lt;br&gt;0.75&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>-0.7&lt;br&gt;-0.7</td>
<td>2.9&lt;br&gt;2.9</td>
<td>1.13&lt;br&gt;1.13&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>-0.2&lt;br&gt;-0.2&lt;br&gt;P&lt;0.001&lt;br&gt;N.S.</td>
<td>20%&lt;br&gt;21%&lt;br&gt;72%</td>
<td>+1&lt;br&gt;+1&lt;br&gt; +1</td>
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</table>

![Diagram](image-url)
**HER 2 +: 1st line „JACOB“**

---

**JOSHUA: Study design, Phase IIa trial**

**HER2-positive inoperable locally advanced or recurrent and/or metastatic GEJ/GC (IHC3+ or IHC2+ and FISH+, ECOG PS 0 or 1)**

**Primary objectives:**
- Estimate minimum (trough) serum pertuzumab concentration to identify a steady state of 220 µg/ml in 80% of patients
- Safety and tolerability

**Arm A**
- Pertuzumab 840 mg, then 420 mg + X + cisplatin xq 3w + trastuzumab n=15

**Arm B**
- Pertuzumab 840 mg + X + cisplatin xq 3w + trastuzumab n=15

**Dose selection for Phase III study based on PK modelling**

---

**The JACOB Study (BO25114) Design**

**Randomization**
(1:1) n = 700
(approximately 350 per treatment arm)

**Key Eligibility Criteria:**
- HER2-positive metastatic gastric/GEJ adenocarcinoma
- IHC 3+ or IHC 2+/ISH+ (central testing required)
- ECOG PS 0 or 1
- Geographic region: Japan, North America, Europe, Asia (not including Japan), Latin America
- Prior gastrectomy (yes/no)
- HER2 IHC+/ISH+ vs. HER2+/ISH+

**Stratification Factors:**
- Treatment Arm A
  - Cepotibine or SFT + Cisplatin*
- Trastuzumab + Pertuzumab 840 mg IV q3W

**Treatment Arm B**
- Cepotibine or SFT + Cisplatin*
- Trastuzumab + Pertuzumab placebo IV q3W

**Follow-up:**
- Primary Endpoint
  - OS (Event = 502)
- Secondary Endpoints: PFS, QoL, DoS, CBR, Safety

*All dose cycles 8 continuation of chemotherapy is at physician's discretion
* If patients permanently stop study treatment (HER2-negative), they continue to be followed for side effects and cardiac monitoring.
Mono vs. combo: S-1 + Irinotecan vs. Irinotecan

Mono vs. combo: Cis + Irinotecan vs. Irinotecan

Biweekly irinotecan plus cisplatin versus irinotecan alone as second-line treatment for advanced gastric cancer: A randomised phase III trial (TCOG GI-0801/BIRIP trial)

- **BIRIP**
  - significantly prolonged PFS compared with irinotecan alone
  - was tolerated as SLC
  - but did not demonstrate a survival benefit in this trial

Higuchi K et al. Eur J Cancer. 2014 May
Renaissance /FLOT5

AIO

limited metastatic carcinoma of stomach or esophagogastric junction

4x FLOT

R A N D O M I S A T I O N

Arm A
Operation (R0-Resection or max. reduction of metastases)

4x FLOT

4x FLOT

4x FLOT

N=271, HR of 0.65 for overall survival (power: 80%)
Conclusion: first-line chemotherapy

• Combination chemotherapy should be offered to patients
  - adequate performance status
  - adequate organ function

• Doublet chemotherapies are accepted “standard” regimens
  - Platinum + fluoropyrimidine
  - FOLFIRI

• FLOT and modified DCF schedules may be considered in:
  - Locally advanced, unresectable patients
  - Bulky disease

• but before starting 1\textsuperscript{st} Line - consider drugs you will use in further lines
Conclusion: second-line (chemo)therapy

- Second-line therapy improves survival and QoL over BSC alone

- Paclitaxel + ramucirumab
  - the most promising drug combination
  - significant survival benefit over chemotherapy alone

- Single-agent chemotherapy or ramucirumab monotherapy
  - for unfit patients

- Second-line or even third
  - trials/ new agents