“Systemic treatment in early and advanced gastric cancer”

Andrés Cervantes
Professor of Medicine
Classical approach to localised gastric cancer

- Surgical resection
- Pathology assessment and estimation of risk
- Treatment based upon classical TNM stage
- Postoperative chemotherapy of doubtful versus no value
- Postoperative chemoradiation
Meta-analysis of trials involving adjuvant chemotherapy versus surgery alone for gastric cancer-1

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Year</th>
<th>No. trials</th>
<th>No. pts</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hermanns (1)</td>
<td>1993</td>
<td>11</td>
<td>2096</td>
<td>0.88</td>
<td>0.78-1.08</td>
<td>No benefit</td>
</tr>
<tr>
<td>J Clin Oncol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Earle (2)</td>
<td>1999</td>
<td>13</td>
<td>1990</td>
<td>0.80</td>
<td>0.66–0.97</td>
<td>Small survival benefit In N+ patients</td>
</tr>
<tr>
<td>Eur J Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Mari (3)</td>
<td>2000</td>
<td>20</td>
<td>3658</td>
<td>0.82</td>
<td>0.75–.89</td>
<td>Small survival benefit</td>
</tr>
<tr>
<td>Ann Oncol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Janunger (4)</td>
<td>2002</td>
<td>21</td>
<td>3962</td>
<td>0.84</td>
<td>0.74–0.96</td>
<td>Very heterogeneous group of trials</td>
</tr>
<tr>
<td>Eur J Surg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Western</td>
<td></td>
<td></td>
<td></td>
<td>0.96</td>
<td>0.83–1.12</td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td></td>
<td></td>
<td></td>
<td>0.58</td>
<td>0.44–076</td>
<td></td>
</tr>
</tbody>
</table>

Meta-analysis of trials involving adjuvant chemotherapy *versus* surgery alone for gastric cancer-2

<table>
<thead>
<tr>
<th>Meta-analysis</th>
<th>Year</th>
<th>No. trials</th>
<th>No. pts</th>
<th>Odds Ratio</th>
<th>95% CI</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zhao <em>et al.</em> (1) Cancer Investigation</td>
<td>2008</td>
<td>15</td>
<td>3212</td>
<td>0.90</td>
<td>0.84-0.96</td>
<td>Marginal, though significant benefit P: 0.001</td>
</tr>
<tr>
<td>Liu <em>et al.</em> (2) Eur J Surg Oncol</td>
<td>2008</td>
<td>19</td>
<td>2286</td>
<td>0.85</td>
<td>0.80-0.90</td>
<td>Marginal, though significant benefit P&lt;0.0001</td>
</tr>
<tr>
<td>Gastric Group (3) JAMA</td>
<td>2010</td>
<td>17</td>
<td>3871</td>
<td>0.82</td>
<td>0.76-090</td>
<td>P&lt;0.001</td>
</tr>
</tbody>
</table>

Why has adjuvant chemotherapy failed to show any positive effect after surgery in gastric cancer?

- Non standard surgery
- High risk of local relapse
- Chemotherapy nor very active in advanced disease: Complete response rate less than 10%
- Heterogeneous samples, low size samples, most patients n-
- Inadequate statistical design
- Prolonged and slow accrual
Overall survival estimate after any chemotherapy or surgery alone truncated at 10 years

Redrawn from The Gastric Group. JAMA 2010;303:1729–37
Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy versus surgery alone: 5-year follow-up of a randomised phase III trial

Adjuvant capecitabine plus oxaliplatin for gastric cancer after D2 gastrectomy versus surgery alone: 5-year follow-up of a randomised phase III trial

The role of radiation in the postoperative setting: Adjuvant chemoradiotherapy for gastric cancer after surgery versus surgery alone: A randomised Phase III Trial

Study design

SURGERY

↓

STRATIFICATION

T 1–4
NODES
0, 1–3, >3

CT+ CT-RT + CT

NO TREATMENT

Adjuvant chemoradiotherapy for gastric cancer after surgery versus surgery alone: A randomised Phase III Trial

Figure 2. Relapse-free Survival among All Eligible Patients, According to Treatment-Group Assignments.
Adjuvant chemoradiotherapy for gastric cancer after surgery versus surgery alone: A randomised Phase III Trial

Figure 1. Overall Survival among All Eligible Patients, According to Treatment-Group Assignment.

Adjuvant chemoradiotherapy for gastric cancer after surgery versus surgery alone: Long term data of a randomised Phase III Trial

**Figure 2.** (A) Overall survival by arm; (B) relapse-free survival by arm. FU, fluorouracil; RT, radiotherapy.
The role of Radiation in the Postoperative Setting
Adjuvant Cisplatin and Capecitabine versus Chemoradiation for Gastric Cancer after Surgery: A Randomized phase III Trial

The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine versus chemoradiation for gastric cancer after surgery: A randomised Phase III Trial

Table 3. Pattern of Recurrence

<table>
<thead>
<tr>
<th>Pattern of Recurrence</th>
<th>XP Arm</th>
<th>XP/XRT/XP Arm</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Locoregional recurrence†</td>
<td>19</td>
<td>8.3</td>
<td>11</td>
</tr>
<tr>
<td>Distant metastasis‡</td>
<td>56</td>
<td>24.6</td>
<td>47</td>
</tr>
</tbody>
</table>

Abbreviations: XP, capecitabine plus cisplatin; XRT, radiotherapy with capecitabine.

The role of Radiation in the Postoperative Setting

Adjuvant Cisplatin and Capecitabine versus Chemoradiation for Gastric Cancer after Surgery: A Randomized phase III Trial

Figure 2. Disease-free survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

Figure 3. Overall survival. XP, capecitabine plus cisplatin; XPRT, concurrent chemoradiotherapy with capecitabine plus cisplatin.

The role of radiation in the postoperative setting: Adjuvant cisplatin and capecitabine versus chemoradiation for gastric cancer after surgery: A randomised Phase III Trial

Localised gastric cancer: Aims of neoadjuvant therapy

- To increase R0 resection rate
- Early treatment of micrometastases
- To reduce locoregional relapses
- Biological studies
Eligible patients:
- Adenocarcinoma of the stomach or lower third of the oesophagus (from 1999), suitable for curative resection
- Non-metastatic disease
- Stage II or greater

Chemotherapy (ECF):
Epirubicin 50 mg/m$^2$, IV day 1
Cisplatin 60 mg/m$^2$, IV day 1
5-FU 200 mg/m$^2$/day, continuous infusion, days 1-21
(cycles repeated every 3 weeks)

Primary
Overall survival

Secondary
Progression-free survival
Surgical resectability
Quality of Life

Recruitment: July 1994-April 2002

MAGIC Trial results

**PFS***
- Logrank p-value = 0.0001
- Hazard Ratio = 0.66
  (95% CI 0.53 - 0.81)

**Overall**
- Logrank p-value = 0.009
- Hazard Ratio = 0.75
  (95% CI 0.60 - 0.93)

<table>
<thead>
<tr>
<th>2 year survival</th>
<th>5 year survival</th>
<th>Median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CSC</strong></td>
<td>50%</td>
<td>36%</td>
</tr>
<tr>
<td><strong>S</strong></td>
<td>41%</td>
<td>23%</td>
</tr>
</tbody>
</table>

**Benefit to CSC arm**
- 9%             | 13%             | 4 mo           |

- On multivariate analysis, treatment effect unchanged after adjustment for age, performance status, site of primary and gender
- Hazard ratio for death
  - Adjusted: 0.74 (95% CI: 0.59-0.93)
  - Unadjusted: 0.75

Summary of trials of perioperative chemotherapy for localised gastric cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>CT</th>
<th>No. pts control</th>
<th>No. pts CT</th>
<th>5-year survival control</th>
<th>5-year survival CT</th>
<th>HR (CI at 95%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cunningham N Eng J Med 2006</td>
<td>ECF</td>
<td>253</td>
<td>250</td>
<td>23%</td>
<td>36 %</td>
<td>0.75 (0.60-0.93)</td>
</tr>
<tr>
<td>Ychou J Clin Oncol 2011</td>
<td>CDDP 5-FU</td>
<td>111</td>
<td>113</td>
<td>24%</td>
<td>38%</td>
<td>0.69 (0.50-0.95)</td>
</tr>
</tbody>
</table>

Neoadjuvant chemotherapy in gastric cancer: Conclusions

- Perioperative chemotherapy:
  - Induces downstaging
  - May increase the R0 resection rate
  - Prolongs disease free survival
  - Improves overall survival

- Evidence level I based upon 2 well designed and properly conducted randomised trials
- Preoperative therapy is better tolerated than postoperative
- Localised gastric cancer requires a multidisciplinary team approach
- Further research on biological predictive factors is needed
- Radiotherapy should be considered experimental
Currently recommended approach to localised gastric cancer

- Clinical assessment and staging
- Multidisciplinary team discussion
- Preoperative treatment in all patients with clinical stage II and III
- Surgical resection after chemotherapy
- Pathology assessment and estimation of risk
- Postoperative chemotherapy if tolerated
- Participation in trials
Treatment for localised gastric cancer: What is standard of care?

Algorithm for the management of gastric cancer

- Operable Stage T1N0
  - Consider endoscopic/limited resection
  - Preoperative chemotherapy
    - Surgery
      - Post-operative chemotherapy
- Operable Stage >T1N0
  - Operable Stage >T1N0
    - Surgery
      - Adjuvant chemoradiation
      - Adjuvant chemotherapy

Treatment for localised gastric cancer: Relevant experimental questions

- The addition of Bevacizumab in the neoadjuvant treatment of gastric cancer
- Should Docetaxel-based scheduled should be used in the neoadjuvant treatment of gastric cancer
- The addition of Radiotherapy in the neoadjuvant treatment of gastric cancer
Histologically confirmed, resectable (MDT review) stage Ib-IV adenocarcinoma of the lower oesophagus, OGJ or stomach

Randomised 1:1

**ECX**
- 3 cycles
- 5-6 week break
- Surgery
- 6-10 week break
- ECX
  - 3 cycles

**ECX + Bevacizumab**
- ECX + Bevacizumab
  - 3 cycles
- 6 doses

**Chemotherapy regimens**
- 21-day cycles

**ECX**
- Epirubicin 50mg/m² IV on day 1
- Cisplatin 60mg/m² IV on day 1
- Capecitabine 1250mg/m² PO daily

**ECX + Bevacizumab**
- Bevacizumab 7.5mg/kg IV on day 1 added to each ECX cycle
472 deaths (233 ECX, 239 ECX+B) have been observed

- Median follow-up is 33 months in both arms

### Overall survival

<table>
<thead>
<tr>
<th></th>
<th>ECX</th>
<th>ECX+B</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median OS</td>
<td>33.97 months</td>
<td>34.46 months</td>
</tr>
<tr>
<td>Hazard Ratio</td>
<td>1.067</td>
<td></td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(0.8911 to 1.279)</td>
<td></td>
</tr>
<tr>
<td>Log-rank p-value</td>
<td>0.4784</td>
<td></td>
</tr>
</tbody>
</table>

### 3-year overall survival (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>ECX</th>
<th>ECX+B</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>48.9% (43.6% to 53.8%)</td>
<td>47.6% (42.3% to 52.7%)</td>
</tr>
</tbody>
</table>
FLOT4 Study Design

- Gastric cancer or adenocarcinoma of the gastroesophageal junction type I-III
- Medically and technically operable stages
- T2-4, every N, M0 or every T, N+, M0

Primary endpoint Phase II (n=300): rate of complete pathological remission (pCR)
Primary endpoint for phase III (n=714): OS, HR 0.76, power 80%, two sided p<0.05

4xFLOT - OP - 4xFLOT

FLOT: docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; leucovorin 200 mg/m², d1; oxaliplatin 85 mg/m², d1, every two weeks

3xECF(X) - OP - 3xECF(X)

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
Pathological Remission with ECF/ECX vs. FLOT – Central Evaluation, **ITT group***

<table>
<thead>
<tr>
<th>Pathological regression</th>
<th>ECF/ECX n(%)</th>
<th>FLOT n(%)</th>
<th>P-Value (2-sided)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>N=137</strong></td>
<td><strong>N=128</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete (pCR)</td>
<td>8</td>
<td>20</td>
<td><strong>.015</strong></td>
</tr>
<tr>
<td>Subtotal (pSR)</td>
<td>23</td>
<td>27</td>
<td></td>
</tr>
<tr>
<td>pCR+pSR</td>
<td>31</td>
<td>47</td>
<td><strong>.015</strong></td>
</tr>
<tr>
<td>Partial (pPR)</td>
<td>28</td>
<td>23</td>
<td></td>
</tr>
<tr>
<td>Minor (pMR)</td>
<td>44</td>
<td>45</td>
<td></td>
</tr>
<tr>
<td>No response (pNR)</td>
<td>8</td>
<td>4</td>
<td><strong>3,1</strong></td>
</tr>
<tr>
<td>Not resectable</td>
<td>26</td>
<td>9</td>
<td><strong>7,0</strong></td>
</tr>
</tbody>
</table>

*primary Endpoint phase II

STO3 (ITT) 5.4%
**Schema**

**TOPGEAR**

ELIGIBILITY: RESECTABLE ADENOCARCINOMA OF STOMACH OR GOJ STAGE IB (T1N1) – IIIC, (T3, 4 and/or N +ve)

**Randomisation**

- **Group 1: Control Arm**
  - ECF (or ECX) X 3
  - REPEATED EVERY 21 DAYS

- **Group 2:**
  - ECF (or ECX) X 2
  - REPEATED EVERY 21 DAYS

**Surgery (min. D1+)**

- PREOP CRT
  - 45 Gy +CI 5-FU (or X)

**ECF (or ECX) X 3**

REPEATED EVERY 21 DAYS
Treatment for advanced gastric cancer: What is standard of care? ESMO guidelines

- **Surgery**
  - Re-assess

- **Inoperable or metastatic**
  - **Palliative chemotherapy**
    - **HER-2 negative**
      - Platinum+ fluoropyrimidine-based doublet or triplet regimen
    - **HER-2 positive**
      - Trastuzumab + CF/CX
  - **Best supportive care if unfit for treatment**
  - **Clinical trials if adequate PS**
  - **Consider clinical trials of novel agents**

Treatment for metastatic/unresectable gastric cancer: Active agents in first line

- Based upon superiority trials:
  - 5-FU
  - Cisplatin
  - Docetaxel
  - Trastuzumab

- Based upon non-inferiority trials
  - Oxaliplatin
  - Capecitabine
  - S1
  - Irinotecan

Have we made any progress in the treatment of advanced gastric cancer?

MEDIAN OVERALL SURVIVAL IN ADVANCED GASTRIC CANCER


EOX: Epirubicin/Oxaliplatin/Capecitabine.
FFCD-GERCOR-FNCLCC 03-07 Phase III Study. FOLFIRI vs ECF in advanced gastric cancer

Stratification:
- Measurable or not
- PS WHO 0-1 or 2
- Adj (R)CT or not
- Linitis or not
- Cardial or gastric
- Center

A: ECX until progression; then FOLFIRI 2d line
B: FOLFIRI until progression; then ECX 2d line

ECX: D1 = Epirubicin 50 mg/m² (15 min.), Cisplatin 60 mg/m² (1 h); D2 to 15: Capecitabine 1 g/m² x 2/d. D1 = D21. *Cumulated dose of Epirubicin < 900 mg/m² (max 18 cures)*

FOLFIRI: D1 = Irinotecan 180 mg/m² (90 min) + LV 400 mg/m² (2h), 5FU b 400 mg/m², 5FU c.i. 2400 mg/m² (46h). D1 = D14

Objective I: 1st line Time-to-Treatment Failure (TTF)

Objectives II:
- PFS, OS, (TTF 2nd line)
- Toxicity
- Response rate, QoL*

Objective II: Response Rate (RR), PFS and OS

<table>
<thead>
<tr>
<th></th>
<th>ECF N=209</th>
<th>FOLFIRI n=207</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>TTF (months)</td>
<td>4.2</td>
<td>5.1</td>
<td>0.008</td>
</tr>
<tr>
<td>RR 1st</td>
<td>39.2%</td>
<td>37.8%</td>
<td>n.s.</td>
</tr>
<tr>
<td>RR 2nd</td>
<td>10.1%</td>
<td>13.7%</td>
<td></td>
</tr>
<tr>
<td>PFS (months) Median</td>
<td>5.29</td>
<td>5.75</td>
<td>0.96</td>
</tr>
<tr>
<td></td>
<td>4.53-6.31</td>
<td>5.19-6.74</td>
<td></td>
</tr>
<tr>
<td>OS (months) Median</td>
<td>9.49</td>
<td>9.72</td>
<td>0.95</td>
</tr>
<tr>
<td></td>
<td>8.77-11.14</td>
<td>8.54-11.27</td>
<td></td>
</tr>
</tbody>
</table>

Phase II Study of modified DCF vs DCF plus G-CSF in advanced gastric cancer

Stratification:
- Measurable or not
- Gastric vs GEJ
- Center

A: modified DCF
B: standard DCF plus G-CSF

Objective: 6 months-PFS
Objectives II:
- RR, OS, Toxicity

Phase II Study of modified DCF vs DCF plus G-CSF in advanced gastric cancer

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose (mg/m²)</th>
<th>Schedule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm A (mDCF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>40</td>
<td>Day 1 IVPB (60 minutes)</td>
</tr>
<tr>
<td>Leucovorin</td>
<td>400</td>
<td>Day 1 IVPB (30 minutes)</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>400</td>
<td>Day 1 IVP</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>1,000 (per day)</td>
<td>IVCI daily × 2 days</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>40</td>
<td>Day 2 or 3 IVPB (30 minutes)</td>
</tr>
<tr>
<td>Arm B (parent DCF plus G-CSF)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel</td>
<td>75</td>
<td>Day 1 IVPB (60 minutes)</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>75</td>
<td>Day 1 IVPB (60 minutes)</td>
</tr>
<tr>
<td>Fluorouracil</td>
<td>750 (per day)</td>
<td>IVCI daily × 5 days</td>
</tr>
<tr>
<td>Neulasta*</td>
<td>6 mg</td>
<td>Subcutaneous on day 8, 9, or 10</td>
</tr>
<tr>
<td>Neupogen*</td>
<td>300 or 480 µg†</td>
<td>Subcutaneous × 7 days (days 10 to 17)</td>
</tr>
</tbody>
</table>

Phase II Study of modified DCF vs DCF plus G-CSF in advanced gastric cancer

Docetaxel + Oxaliplatin + 5FU-LV/Capecitabine
TE vs TEF vs TEX

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Patients nr</th>
<th>RR %</th>
<th>95% CI</th>
<th>PFS months</th>
<th>95% CI</th>
<th>OS months</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>TE</td>
<td>79</td>
<td>23,1</td>
<td>14,3-34,0</td>
<td>4,50</td>
<td>3,68-5,32</td>
<td>8,97</td>
<td>7,79-10,9</td>
</tr>
<tr>
<td>TEX</td>
<td>86</td>
<td>25,6</td>
<td>16,6-36,6</td>
<td>5,55</td>
<td>4,30-6,37</td>
<td>11,30</td>
<td>8,08-14,0</td>
</tr>
<tr>
<td>TEF</td>
<td>89</td>
<td>46.6</td>
<td>35,9-57,5</td>
<td>7,66</td>
<td>6,97-9,40</td>
<td>14,59</td>
<td>11,7-21,8</td>
</tr>
</tbody>
</table>

Targeted therapies in first-line treatment for advanced gastric cancer: Summary of Phase III Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Chemotherapy</th>
<th>Biological</th>
<th>HR OS</th>
<th>P value</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA(^1)</td>
<td>Cisplatin+5-FU/capecitabine</td>
<td>Trastuzumab</td>
<td>0.74</td>
<td>0.04</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>AVAGAST(^2)</td>
<td>Cisplatin+capecitabine</td>
<td>Bevacizumab</td>
<td>0.87</td>
<td>0.10</td>
<td>+2.0 months</td>
</tr>
<tr>
<td>EXPAND(^3)</td>
<td>Cisplatin+capecitabine</td>
<td>Cetuximab</td>
<td>1.00</td>
<td>0.95</td>
<td>-1.3 months</td>
</tr>
<tr>
<td>REAL-3(^4)</td>
<td>Oxaliplatin+epirubicin+capecitabine</td>
<td>Panitumumab</td>
<td>1.37</td>
<td>0.013</td>
<td>-2.5 months</td>
</tr>
<tr>
<td>RILOMET-1(^5)</td>
<td>Cisplatin+epirubicin+capecitabine</td>
<td>Rilotumumab</td>
<td>--</td>
<td>--</td>
<td>Stopped in futility analysis</td>
</tr>
<tr>
<td>METGASTRIC(^6)</td>
<td>FOLFOX6</td>
<td>Onartuzumab</td>
<td>1.06</td>
<td>0.83</td>
<td>-0.6 months</td>
</tr>
</tbody>
</table>

Targeted therapies against HER2 in advanced gastric cancer: Summary of Phase III Trials on lapatinib

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>Chemotherapy backbone</th>
<th>Line of therapy number</th>
<th>HR</th>
<th>P</th>
<th>Response rate</th>
<th>Increase in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>ToGA¹</td>
<td>Cisplatin+5-FU/capecitabine</td>
<td>First 584</td>
<td>0.74</td>
<td>0.04</td>
<td>51% vs 37%  p=0.0017</td>
<td>+2.8 months</td>
</tr>
<tr>
<td>LOGiC²</td>
<td>Oxaliplatin/capecitabine</td>
<td>First 545</td>
<td>0.91</td>
<td>0.35</td>
<td>53% vs 39%  p=0.031</td>
<td>+1.7 months</td>
</tr>
<tr>
<td>TyTAN³</td>
<td>Paclitaxel</td>
<td>Second 261</td>
<td>0.84</td>
<td>0.20</td>
<td>27% vs 9%  p=0.001</td>
<td>+2.1 months</td>
</tr>
</tbody>
</table>

### Gastric cancer: Second line chemotherapy. Trials comparing BSC versus active treatment

<table>
<thead>
<tr>
<th>Trial author</th>
<th>Year</th>
<th>Patients random (n)</th>
<th>Treatment</th>
<th>Response rate (%)</th>
<th>HR OS</th>
<th>P value</th>
<th>Gain in median survival</th>
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<tbody>
<tr>
<td>Thuss-Patience, et al.¹</td>
<td>2011</td>
<td>40 1:1</td>
<td>Irinotecan</td>
<td>NR SD 58%</td>
<td>0.48</td>
<td>0.0023</td>
<td>2.4 months</td>
</tr>
<tr>
<td>Kang, et al.²</td>
<td>2012</td>
<td>193 2:1</td>
<td>Irinotecan Docetaxel</td>
<td>NR</td>
<td>0.65</td>
<td>0.004</td>
<td>1.3 months</td>
</tr>
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<td>Ford, et al.³</td>
<td>2014</td>
<td>168 1:1</td>
<td>Docetaxel</td>
<td>NR</td>
<td>0.67</td>
<td>0.01</td>
<td>1.6 months</td>
</tr>
</tbody>
</table>

Gastric cancer second line chemotherapy: Docetaxel vs BSC (COUGAR-02 Trial) is improving survival

Figure 2: Kaplan-Meier plot of overall survival

Gastric cancer: Second line chemotherapy trials comparing BSC versus active treatment

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<th>Trial author</th>
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<td>Otshu, et al.⁴</td>
<td>2013</td>
<td>656 2:1</td>
<td>Everolimus</td>
<td>0.90</td>
<td>0.124</td>
<td>0.9 months</td>
</tr>
<tr>
<td>Fuchs, et al.⁵</td>
<td>2014</td>
<td>355 2:1</td>
<td>Ramucirumab</td>
<td>0.77</td>
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Gastric cancer: Second line chemotherapy trials comparing BSC versus active treatment

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<td>Ramucirumab</td>
<td>0.77</td>
<td>0.047</td>
<td>1.4 months</td>
</tr>
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## Gastric cancer: Second line and third line trials comparing BSC versus active treatment

<table>
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<th>Patients random (n)</th>
<th>Treatment</th>
<th>HR OS</th>
<th>P value</th>
<th>Gain in median survival</th>
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<td>2014</td>
<td>168 1:1</td>
<td>Docetaxel</td>
<td>0.67</td>
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<td>Ramucirumab</td>
<td>0.77</td>
<td>0.047</td>
<td>1.4 months</td>
</tr>
<tr>
<td>Li, et al.⁶</td>
<td>2016</td>
<td>273 2:1</td>
<td>Apatinib</td>
<td>0.70</td>
<td>0.015</td>
<td>1.8 months</td>
</tr>
</tbody>
</table>

Gastric cancer second line treatment: Ramucirumab vs BSC (REGARD Trial) is improving survival

Gastric cancer: Second line chemotherapy trials comparing two active treatments

<table>
<thead>
<tr>
<th>Trial author</th>
<th>Year</th>
<th>Patients (n)</th>
<th>Treatment</th>
<th>HR OS</th>
<th>P value</th>
<th>Gain in median survival</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hironaka, et al.¹</td>
<td>2013</td>
<td>223</td>
<td>Irinotecan vs paclitaxel</td>
<td>1.13</td>
<td>0.38</td>
<td>0.9 months for irinotecam</td>
</tr>
<tr>
<td>Wilke et al.²</td>
<td>2014</td>
<td>665</td>
<td>Paclitaxel+/-ramucirumab</td>
<td>0.80</td>
<td>0.017</td>
<td>2.2 months</td>
</tr>
</tbody>
</table>

Gastric cancer second line treatment: Addition of ramucirumab to paclitaxel improves overall survival (Rainbow Trial)

Phase II Study of weekly Paclitaxel +/- Olaparib for second line in advanced gastric cancer

Stratification: ATM Low

- A: weekly Paclitaxel
- B: weekly Paclitaxel plus Olaparib 100 mg bid

- Primary end point: PFS
- Co-Primary end point: PFS in ATM Low
- Secondary end points: OS, OS in ATM Low, Toxicity

Phase II Study of weekly Paclitaxel +/- Olaparib for second line in advanced gastric cancer

Phase II Study of weekly Paclitaxel +/- Olaparib for second line in advanced gastric cancer

Pembrolizumab induces responses in chemorefractory gastric cancer

<table>
<thead>
<tr>
<th></th>
<th>Investigator review</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 39</td>
</tr>
<tr>
<td>ORR, % (95% CI)</td>
<td>22.2 (10.1, 39.2)</td>
</tr>
<tr>
<td>Best overall response, n (%)</td>
<td></td>
</tr>
<tr>
<td>Complete response(^b)</td>
<td>0</td>
</tr>
<tr>
<td>Partial response(^b)</td>
<td>8 (22.2)</td>
</tr>
<tr>
<td>Stable disease</td>
<td>5 (13.9)</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>19 (52.8)</td>
</tr>
<tr>
<td>No assessment(^c)</td>
<td>1 (2.8)</td>
</tr>
<tr>
<td>Not determined(^d)</td>
<td>3 (8.3)</td>
</tr>
</tbody>
</table>

Muro K, et al. ASCO GI 2015; Abstract nr.03
Classification of gastric adenocarcinoma: Pathology

- Intestinal versus diffuse subtypes

Classification of Gastric Adenocarcinoma: Pathology

- Papillary carcinomas
- Tubular carcinomas
- Mucinous carcinomas
- Poorly cohesive carcinomas

WHO Classification of Tumours of the Digestive System 4th Ed.2010 (International Agency for Cancer Research)
Comprehensive Molecular Characterization of Gastric Adenocarcinoma: Molecular platforms

- Array-based somatic copy number analysis
- Whole exome sequencing
- Array-based DNA methylation profiling
- Messenger RNA sequencing
- microRNA sequencing
- Reverse Phase Protein Array (RPPA)

Comprehensive Molecular Characterization of Gastric Adenocarcinoma: Molecular platforms
Comprehensive Molecular Characterization of Gastric Adenocarcinoma: PI3KCA mutations by subtype

Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes

Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes.
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Molecular analysis of gastric cancer identifies subtypes associated with distinct clinical outcomes.

Advanced Oesophago-Gastric cancer: Take-home messages I

- Her2 status to be determined in all patients with advanced disease
- Trastuzumab to be added if HER2 positive (+++)
- Platinum-based chemotherapy as first option, with FOLFIRI as an alternative
- Second line chemotherapy also prolongs survival in good PS patients
- Ramucirumab as single agent prolongs survival versus BSC
- Ramucirumab in combination with paclitaxel improves outcomes over paclitaxel
Advanced Oesophago-Gastric cancer: Take-home message II

- Most targeted therapies failed in molecularly unselected trials
- Immunotherapy (Pembrolizumab) under development with interesting data to be confirmed
- Better selection of patients needed in clinical trials
- Validation of molecular classification in trials
- International cooperation