Chemotherapy for metastatic gastric cancer

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Disclosure

• Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, MSD, Merck Serono, Gilead Science, Bayer, Novartis

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• Honorarium: Taiho, Pfizer, Amgen, Eli-Lilly
Continuum of care

Cisplatin + 5-FU
Oxaliplatin + Capecitabine

6-8 cycles
OR
till disease progression
Overall survival with chemotherapy in advanced OG cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Months</th>
</tr>
</thead>
<tbody>
<tr>
<td>BSC</td>
<td>3</td>
</tr>
<tr>
<td>FAMTX</td>
<td>6.7</td>
</tr>
<tr>
<td>CF</td>
<td>8.6</td>
</tr>
<tr>
<td>IF</td>
<td>9</td>
</tr>
<tr>
<td>ECF</td>
<td>9.9</td>
</tr>
<tr>
<td>EOF</td>
<td>9.9</td>
</tr>
<tr>
<td>DCF</td>
<td>9.2</td>
</tr>
<tr>
<td>XP</td>
<td>10.5</td>
</tr>
<tr>
<td>ECX</td>
<td>9.9</td>
</tr>
<tr>
<td>EOX</td>
<td>11.2</td>
</tr>
<tr>
<td>FC+T</td>
<td>13.8</td>
</tr>
</tbody>
</table>

Population based treatment in metastatic gastric cancer

- Dutch Eindhoven Cancer Registry data
- Between 1990 and 2011
- N=4,797 in a catchment population of ~2.4 million

Prescription of chemotherapy for patients with metastatic gastric cancer over time, 1990–2011

Overall survival over different time periods

Bernards et al Ann Oncol 2013
Phase III capecitabine global registration in AGC trial design (ML 17032)

XP
Cisplatin 80mg/m² iv D1
Capecitabine 2000mg/m²/day D1-14
Treatment given every 3 weeks

n=160

FP
Cisplatin 80mg/m² iv D1
5-FU 800mg/m²/day D1-5
Treatment given every 3 weeks

n=156

Primary objective: non-inferiority in PFS with XP

Kang et al Ann Oncol 2009
Progression free survival (ML17032)

- Estimated probability
- Median PFS months (95% CI)
  - XP (n=139): 5.6 (4.9–7.3)
  - FP (n=137): 5.0 (4.2–6.3)
- HR=0.81 (95% CI: 0.63–1.04)
  - Compared to HR upper limit 1.25, p<0.001

Per protocol analysis

Kang et al Ann Oncol 2009
Overall survival (ML17032)

Estimated probability

- **Median OS months (95% CI)**
  - XP (n=139): 10.5 (9.3–11.2)
  - FP (n=137): 9.3 (7.4–10.6)

- **HR=0.85 (95% CI: 0.64–1.13)**
- Compared to HR upper limit 1.25, p=0.008

Per protocol analysis

Kang et al Ann Oncol 2009
REAL-2: first line phase III trial in oesophagogastric cancer

Epirubicin 50mg/m² day 1
Cisplatin 60mg/m² vs oxaliplatin 130mg/m² day 1
5-FU 200mg/m²/day continuous infusion vs Capecitabine 500–625mg/m² twice daily continuous
For 24 weeks: eight cycles every 3 weeks

Overall Survival (Per-protocol): Fluoropyrimidine comparison

<table>
<thead>
<tr>
<th>Fluoropyrimidine</th>
<th>N</th>
<th>Median OS</th>
<th>1-year OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU</td>
<td>484</td>
<td>9.6 months</td>
<td>39.4% (35.0-44.0)</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>480</td>
<td>10.9 months</td>
<td>44.6% (40.1-49.0)</td>
</tr>
</tbody>
</table>

HR = 0.86 (95% CI: 0.75 – 0.99)

Number at risk

<table>
<thead>
<tr>
<th>Fluoropyrimidine</th>
<th>N</th>
<th>1-year</th>
<th>2-year</th>
<th>3-year</th>
<th>4-year</th>
<th>5-year</th>
</tr>
</thead>
<tbody>
<tr>
<td>5FU</td>
<td>484</td>
<td>178</td>
<td>37</td>
<td>8</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>480</td>
<td>206</td>
<td>52</td>
<td>12</td>
<td>3</td>
<td>1</td>
</tr>
</tbody>
</table>

REAL 2 overall survival
ECF vs EOX (ITT)

Median OS 1-year OS (95% CI)
ECF 9.9 months 37.7% (31.8–43.6)
EOX 11.2 months 46.8% (40.4–52.9)

HR=0.80 (95% CI: 0.66 - 0.97)
Log rank p = 0.02

REAL 2/ML17032 meta-analysis (n=1,318)

Log-rank Test: $p = 0.027$

Hazard Ratio: $0.87$ (95% CI: $0.77-0.98$)

Median Overall Survival:
- **5-FU**: 9.4 months
- **Capecitabine**: 10.6 months

Oral fluoropyrimidines

Xeloda® 500 mg
film-coated tablets
Capecitabine

Xeloda® 150 mg
film-coated tablets
Capecitabine
# Japanese first line randomised phase III studies of S-1 in advanced gastric cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>n</th>
<th>RR (%)</th>
<th>mPFS (months)</th>
<th>mOS (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>JCOG 9205¹</td>
<td>CI 5-FU</td>
<td>105</td>
<td>11.4</td>
<td>1.9</td>
<td>7.1</td>
</tr>
<tr>
<td></td>
<td>5-FU + Cisplatin</td>
<td>105</td>
<td>34.3</td>
<td>3.9</td>
<td>7.3</td>
</tr>
<tr>
<td>JCOG 9912²</td>
<td>CI 5-FU</td>
<td>234</td>
<td>9</td>
<td>2.9</td>
<td>10.8</td>
</tr>
<tr>
<td></td>
<td>S-1</td>
<td>234</td>
<td>28</td>
<td>4.2</td>
<td>11.4</td>
</tr>
<tr>
<td></td>
<td>Irinotecan + Cisplatin</td>
<td>236</td>
<td>38</td>
<td>4.8</td>
<td>12.3</td>
</tr>
<tr>
<td>SPIRITS³</td>
<td>S-1</td>
<td>150</td>
<td>31</td>
<td>4.0</td>
<td>11.0</td>
</tr>
<tr>
<td></td>
<td>S-1 + Cisplatin</td>
<td>149</td>
<td>54</td>
<td>6.0</td>
<td>13.0</td>
</tr>
<tr>
<td>GC0301/</td>
<td>S-1</td>
<td>162</td>
<td>26.9</td>
<td>3.6</td>
<td>10.5</td>
</tr>
<tr>
<td>TQP-002⁴</td>
<td>S-1 + Irinotecan</td>
<td>164</td>
<td>41.5</td>
<td>4.5</td>
<td>12.8</td>
</tr>
</tbody>
</table>

Phase III S-1 global registration in AGC trial design (FLAGS)

**R**

- **CS**
  - Cisplatin 75mg/m² iv D1
  - S-1 25mg/m²/twice day D1-21
  - Treatment given every 4 weeks
  - n=527

- **CF**
  - Cisplatin 100mg/m² iv D1
  - 5-FU 1000mg/m²/day D1-5
  - Treatment given every 4 weeks
  - n=526

Primary objective: superiority in OS with CS

Ajani et al. J Clin Oncol 2010
Overall survival (FLAGS)

Log-rank test $P = .1983$
Hazard ratio: 0.92 (95% CI, 0.80 to 1.05)
Median (months): CS 8.6, CF 7.9

No. at risk
S-1 521 341 172 69 24 4
FU 508 326 156 56 19 3

Ajani et al. J Clin Oncol 2010
## Overall survival non-inferiority comparisons

<table>
<thead>
<tr>
<th>Study/Treatment comparisons</th>
<th>N</th>
<th>Hazard Ratios (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>REAL 2</strong>¹</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine vs. 5-FU</td>
<td>1,002</td>
<td>0.86 (0.75-0.99)</td>
</tr>
<tr>
<td><strong>ML17032</strong>²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine vs. 5-FU</td>
<td>316</td>
<td>0.85 (0.64-1.13)</td>
</tr>
<tr>
<td><strong>FLAGS</strong>³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S-1 vs. 5-FU</td>
<td>1,029</td>
<td>0.92 (0.80-1.05)</td>
</tr>
<tr>
<td><strong>REAL2/ML17032 meta-analysis</strong>⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Capecitabine vs. 5-FU</td>
<td>1,318</td>
<td>0.87 (0.77-0.98)</td>
</tr>
</tbody>
</table>

Randomised phase III onartuzumab (MetMAb) in advanced gastric cancer trial design (METGastric)

**Advanced OGJ or gastric adeno-carcinoma**

50% of tumour cells showing weak, moderate and/or strong staining intensity

**Co-primary endpoint:** Overall survival (ITT population)

Overall survival (Met-IHC 2+ or 3+ subgroup)

FOLFOX + placebo
Treatment given every 14 days

FOLFOX + onartuzumab
Treatment given 14 days

n=283
n=279

Shah et al ASCO 2015
Overall survival

Intention-to-treat

HR: 0.82
95% CI: 0.59, 1.15
p=0.24

MET 2+/3+

HR: 0.64
95% CI: 0.40, 1.03
p=0.062

Shah et al ASCO 2015
Phase III docetaxel trial design (TAX 325)

DCF
Docetaxel 75mg/m² iv D1
Cisplatin 75mg/m² iv D1
5-FU 750/m²/day D1-5

CF
Cisplatin 100mg/m² iv D1
5-FU 1000mg/m²/day D1-5

n=227
n=230

Primary objective: superior TTP with DCF relative to CF

Van Cutsem et al J Clin Oncol 2006
**TAX 325 survival**

### Time to Progression

- **DCF**
  - Probability (%)
  - Median: 5.6 months
  - Log-rank $P \leq .001$

- **CF**
  - Probability (%)
  - Median: 3.7 months

### Overall Survival

- **DCF**
  - Probability (%)
  - Median: 9.2 months
  - Log-rank $P = .02$

- **CF**
  - Probability (%)
  - Median: 8.6 months

<table>
<thead>
<tr>
<th></th>
<th>DCF</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>RR</td>
<td>37%</td>
<td>25%</td>
</tr>
<tr>
<td>TTP</td>
<td>5.6 months</td>
<td>3.7 months</td>
</tr>
<tr>
<td>OS</td>
<td>9.2 months</td>
<td>8.6 months</td>
</tr>
</tbody>
</table>

Van Cutsem et al J Clin Oncol 2006
TAX325: increased febrile neutropenia with DCF

% patients with grade 3/4

Neutropenia
- DCF: 82%
- CF: 57%

Febrile neutropenia, infection
- DCF: 29%
- CF: 12%

Anemia
- DCF: 10%
- CF: 5%

Platelets
- DCF: 2%
- CF: 2%

Van Cutsem et al J Clin Oncol 2006
Continuum of care

HER2 +ve Trastuzumab
Cisplatin
Oxaliplatin
5-FU
Capecitabine

6-8 cycles
OR
till disease progression
Phase III trastuzumab global registration in AGC trial design (TOGA)

Locally advanced or metastatic HER2 positive adenocarcinoma of OGJ and stomach

**Cisplatin + 5FU/capecitabine (FC)**

n=290

**FC** + trastuzumab

n=294

**Progression free survival**

- ORR
  - FC: 35%
  - FC + Trastuzumab: 47.0%
  - p=0.0017

**Overall survival**

*88% of patients received capecitabine

Bang et al The Lancet 2010
Continuum of care

Cisplatin + 5-FU
Oxaliplatin + Capecitabine

6-8 cycles OR till disease progression

Rechallenge with platinum/FP

If long progression free interval (at least >3 months) after first line therapy
Rechallenge with platinum/fluoropyrimidine (PF)

Treated with PF
n=950

Progressed >3 months after completing therapy
n=298 (31%)

Rechallenged with PF chemotherapy
n=106 (11%)

Median PFS from rechallenge 3.9 months
Median OS from rechallenge 6.6 months

Okines et al. Oncology 2010
Continuum of care

Cisplatin + Oxaliplatin + 5-FU + Capecitabine

6-8 cycles
OR
till disease progression

Docetaxel, Paclitaxel, Irinotecan
Two pivotal RCTs establishing second- or subsequent-line therapy for gastric cancer

Korean study\(^1\)

HR 0.657; 95%CI 0.485, 0.891; one-sided p=0.007

COUGAR-02\(^2\)

HR 0.67; 95%CI 0.49, 0.92; p=0.01

ASC, active symptom control; BSC, best supportive care; CI, confidence interval; HR, hazard ratio; RCT, randomised controlled trial; SLC, salvage chemotherapy.

Overall survival with second-line chemotherapy in advanced oesophago-gastric cancer

- **Docetaxel**: 5.2 months
- **BSC**: 3.6 months
- **Docetaxel/Irino**: 5.3 months
- **BSC**: 3.8 months
- **Irinotecan**: 4.0 months
- **BSC**: 2.4 months

BSC, best supportive care.

Overall survival with second-line chemotherapy in advanced oesophago-gastric cancer: meta-analysis of patient-level data


HR: 0.63; 95% CI: 0.51-0.77
p<0.0001
Overall survival with second-line chemotherapy in advanced oesophago-gastric cancer: meta-analysis of patient-level data

Docetaxel
  Ford et al. 2014

Kang et al. 2012

Stratified
  Interaction between 2 groups: $\chi^2=0.0$, $P=0.85$

Irinotecan
  Thuss-Patience et al. 2011
  Kang et al. 2012

Stratified
  Interaction between 2 groups: $\chi^2=0.0$, $P=0.88$

Overall

SC: Supportive care.

Janowitz et al Br J Cancer 2016
Phase III randomised trial of second-line paclitaxel vs. irinotecan in AGC (WJOG 4007) trial

n=111  Weekly paclitaxel
Paclitaxel (80 mg/m²) D1, 8 and 15 q4w

n=112  Biweekly irinotecan
Irinotecan (150 mg/m²) D1 and 15 q4w

**Progression-free survival**

- Log-rank $P = .33$

**Overall survival**

- Log-rank $P = .38$

<table>
<thead>
<tr>
<th>ORR</th>
<th>Paclitaxel</th>
<th>Irinotecan</th>
<th>$p=0.24$</th>
</tr>
</thead>
<tbody>
<tr>
<td>20.9%</td>
<td>13.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Royal Marsden Hospital second line paclitaxel use

ORR = 18%; Disease control rate = 49%

Overall survival

Progression free survival

Median OS = 5.8 months
(95% CI: 4.8 – 6.8 months)

Median PFS = 2.6 months
(95% CI: 1.9 – 3.2 months)

Median OS from start of first line chemotherapy: 14.3 months
2 yr OS: 25.9%; 3 yr OS: 13.3%

Continuum of care

Cisplatin + 5-FU
Oxaliplatin + Capecitabine

6-8 cycles
OR
till disease progression

Docetaxel  Paclitaxel  Irinotecan
Phase III FFCD-Unicancer-GERCOR study

n=209  \[ \text{ECX} \rightarrow \text{FOLFIRI} \]

n=207  \[ \text{FOLFIRI} \rightarrow \text{ECX} \]

Primary objective: Time-to-treatment failure (TTF) for the first-line therapy in the two treatment arms defined as the time between random assignment and disease progression, treatment discontinuation, or death

ECX: Epirubicin 50 mg/m² D1; Cisplatin 60 mg/m² D1;
Capecitabine 1 g/m² twice daily D2-15 Q3W

FOLFIRI: Irinotecan 180 mg/m²; LV 400 mg/m²; 5-FU 400 mg/m² IV bolus; 5-FU 2,400 mg/m² CI over 46 hours Q2W

Guimbaud et al J Clin Oncol 2014
Phase III FFCD-Unicancer-GERCOR study
Time to treatment failure

HR, 0.77; 95% CI, 0.63 to 0.93; P = .008

<table>
<thead>
<tr>
<th></th>
<th>ECX</th>
<th>FOLFIRI</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS</td>
<td>5.29</td>
<td>5.75</td>
</tr>
<tr>
<td>HR</td>
<td>0.99 (95% CI 0.81, 1.21); p=0.96</td>
<td></td>
</tr>
<tr>
<td>mOS</td>
<td>9.49</td>
<td>9.72</td>
</tr>
<tr>
<td>HR</td>
<td>1.01 (95% CI 0.82, 1.24); p=0.95</td>
<td></td>
</tr>
</tbody>
</table>

Guimbaud et al J Clin Oncol 2014
Continuum of care

- Cisplatin
- Oxaliplatin
- 5-FU
- Capecitabine

6-8 cycles
OR
till disease progression

- Docetaxel
- Paclitaxel
- Irinotecan

Peripheral neuropathy
Continuum of care

HER2 +ve
Trastuzumab

Cisplatin
Oxaliplatin

5-FU
Capecitabine

Docetaxel
Paclitaxel
Irinotecan

6-8 cycles
OR
till disease progression

Peripheral neuropathy
GI tox and infection
**Grades 3–4 adverse events in second- or subsequent-line cytotoxic drug RCT in gastric cancer**

<table>
<thead>
<tr>
<th>Toxicities</th>
<th>AIO(^1)</th>
<th>Korean(^2)</th>
<th>*COUGAR-02(^3)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>IRI (N=19)</td>
<td>IRI (N=60)</td>
<td>DOC (N=66)</td>
</tr>
<tr>
<td>Neutropenia, %</td>
<td>21</td>
<td>18</td>
<td>15</td>
</tr>
<tr>
<td>Febrile neutropenia, %</td>
<td>16</td>
<td>2(^†)</td>
<td>2(^†)</td>
</tr>
<tr>
<td>Anaemia, %</td>
<td>11</td>
<td>32</td>
<td>30</td>
</tr>
<tr>
<td>Thrombocytopenia, %</td>
<td>0</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>Infection, %</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Diarrhoea, %</td>
<td>26</td>
<td>8</td>
<td>3</td>
</tr>
<tr>
<td>Nausea, %</td>
<td>5</td>
<td>3</td>
<td>5</td>
</tr>
<tr>
<td>Vomiting, %</td>
<td>5</td>
<td>NR</td>
<td>NR</td>
</tr>
</tbody>
</table>

*21% had \(^*\) grade 4 toxicity with docetaxel versus 4% with BSC;  
\(^†\)6 episodes of febrile neutropenia in both IRI and DOC arms;  
\(^‡\)COUGAR-02 reported all GI toxicities as a composite endpoint.  
BSC, best supportive care; DOC, docetaxel; IRI, irinotecan; NR, not reported.

\(^1\)Thuss-Patience et al. Eur J Cancer 2011;  
\(^2\)Kang et al. J Clin Oncol 2012;  
\(^3\)Ford et al. Lancet Oncol 2014
German AIO QoLiTaX trial

- Multicentre cohort study
- Between 2008 and 2011, 2,659 patients treated with docetaxel-based chemotherapy were included
- The strongest effect of global health status/QoL average scores was seen by the following order of Grade 3 or 4 toxicities (%):
  - Diarrhoea (50.9 vs. 33.1)
  - Vomiting (50.9 vs. 35.2)
  - Dyspnoea (50.9 vs. 35.8)
  - Mucositis/stomatitis (50.9 vs. 36.4)
  - Nausea (50.9 vs. 36.7)
  - Infection (50.9 vs. 37.1)
  - Fatigue (50.9 vs. 43.8)
  - Anaemia (50.9 vs. 41.0)
- p<0.05 for all comparisons

QoL, quality of life.

Continuum of care

HER2 +ve
Trastuzumab

Cisplatin
Oxaliplatin

5-FU
Capecitabine

6-8 cycles
OR
till disease progression

Docetaxel
Paclitaxel
Irinotecan

Peripheral neuropathy

GI tox and infection
Continuum of care

HER2 +ve
Trastuzumab

Cisplatin
Oxaliplatin

5-FU
Capecitabine

6-8 cycles
OR
till disease progression

Rechallenge
with platinum/FP

Peripheral neuropathy

G1 tox and infection

Docetaxel

Paclitaxel
+ Ramucirumab

? apatinib

Maintenance therapy

PD-1 antibody
± other IO
± anti-angiogenics
± cytotoxics
± other targeted therapy
Case based discussion
Case history 1

- 68 years old female
- Jun 15 presented with hiccups and progressive dysphagia
- Aug 15 endoscopy showed moderately differentiated adenocarcinoma at the gastro-oesophageal junction HER2 negative
- CT scans showed peritoneal metastases
- PS=1
What treatment would you recommend?

1) Cisplatin + capecitabine
2) Oxaliplatin + capecitabine
3) Cisplatin + S-1 or SOX
4) ECX or EOX
5) (Modified) DCF
6) FLOT
7) FOLFIRI
8) Clinical trial

Speaker’s own contribution
Case history 1

- Started on EOX (epirubicin, oxaliplatin and capecitabine)
- Disease progression after 4 cycles of chemotherapy with new biopsy proven subcutaneous metastases
- Persistent grade 1 peripheral neuropathy
- PS = 1
What treatment would you recommend?

1) Palliative care alone – palliative radiotherapy to symptomatic subcutaneous metastases
2) Paclitaxel or docetaxel
3) Paclitaxel + ramucirumab
4) Ramucirumab alone
5) Irinotecan
6) Clinical trials
RMH sponsored second or subsequent line OG cancer studies

Biomarker evaluation during first line and maintenance treatment

Biomarker enrichment and selection

- ATM deficient
  - OPERA
    - Paclitaxel
    - Olaparib
  - Pachtaxel
- c-MYC amplified
  - I-MYC
    - Ibrutinib
- Plasma FGFR amplified
  - FGFR study
    - AZ 4547
- Unselected may enrich later
  - LISTEN
    - Lucitanib
    Selective inhibitor to FGFR1-3, VEGFR1-3, PDGFRα/β
Acknowledgement

National Health Service funding to the National Institute for Health Research Biomedical Research Centre