CHEMOTHERAPY FOR METASTATIC GASTRIC CANCER

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ESMO Gastric Cancer Preceptorship Valencia 2017
Honoraria for advisory role
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IMPORTANT CONSIDERATIONS WHEN TREATING ADVANCED GASTRIC CANCER

Impact of treatment on QoL

Impact of gastric cancer on QoL

- Pain
- Anorexia
- Dysphagia
- Weight loss

Impact of gastric cancer on QoL

- Short OS
- Neopatthy
- Nausea
- Fatigue

- Chemotherapy response in 30-50% patients
- Relief of symptoms
- OS

Most patients are symptomatic
Median OS with BSC is approximately 4m

Chemotherapy response in 30-50% patients
Median OS with 1st line chemo is <1 year

BSC, Best Supportive care; OS, overall survival; QoL, quality of life
1. Is chemotherapy better than no treatment?
2. Is combination chemotherapy more effective?
3. What is the role of doublet vs. triplet chemotherapy?
4. Drug substitutions
   - Cisplatin vs oxaliplatin
   - 5FU vs capecitabine vs S1
   - Irinotecan for platinum
5. What is the benefit of second line chemotherapy?

CHEMOTHERAPY FOR METASTATIC GASTRIC CANCER

Is palliative chemotherapy better than best supportive care?

FAMTX > BSC

1993 1995 1997 2017

FAMTX > BSC

ELF ↑ QoL vs BSC

FAMTX, 5-FU doxorubicin, and methotrexate; FEMTX, 5-FU epirubicin, and methotrexate; ELF, etoposide, leucovorin, 5FU

## CHEMOTHERAPY VS BSC TRIALS IN GASTRIC CANCER

<table>
<thead>
<tr>
<th>TRIAL</th>
<th>n</th>
<th>ORR (%)</th>
<th>OS (m)</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Murad et al 1993</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAMTX</td>
<td>30</td>
<td>50</td>
<td>12.3</td>
<td>0.0006</td>
</tr>
<tr>
<td>BSC</td>
<td>10</td>
<td></td>
<td>3.1</td>
<td></td>
</tr>
<tr>
<td>Pyrhönen et al 1995</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FEMTX</td>
<td>21</td>
<td>29</td>
<td>9</td>
<td>0.001</td>
</tr>
<tr>
<td>BSC</td>
<td>20</td>
<td></td>
<td>3</td>
<td></td>
</tr>
<tr>
<td>Glimelius et al</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ELF or LV (older)</td>
<td>31</td>
<td>NR</td>
<td>8</td>
<td>NS</td>
</tr>
<tr>
<td>BSC</td>
<td>30</td>
<td></td>
<td>5</td>
<td>↑QoL</td>
</tr>
</tbody>
</table>

Cochrane weighted meta-analysis suggests that chemotherapy vs BSC in metastatic gastric cancer lead to an improvement in median OS from 4.3 months to 11 months: 0.37 (95% CI) 0.24 to 0.55).

FAMTX: MTX 1000 mg/m² D1; 5-FU 1500 mg/m² D1; LV 15 mg p.o. q6h D1-2, repeated D29, doxorubicin 30 mg/m² D15, D44
FEMTX: MTX 1500 mg/m² D1, 5-FU 1500 mg/m² D1, LV30 mg p.o. Q6h d 1-2, epirubicin 60 mg/m² D15, repeat D29
ELF: LV 350 mg/m² , etoposide 120 mg/m² and 5-FU 500 mg/ m² , D-1-3 q 3wks

CHEMOTHERAPY FOR METASTATIC GASTRIC CANCER

Selected cisplatin trials


FAMTX, 5-FU doxorubicin, and methotrexate, FEMTX, 5-FU eprubicin, and methotrexate, ELF, etoposide, leucovorin, 5FU ECF, epirubicin, cisplatin, 5FU. ADM, adriamycin. MMC, mitomycin C
Many trials compare the benefit of single agent chemotherapy (mostly 5FU) with doublet and triplet chemotherapy.

Meta-analysis of 23 or these trials (n= 4447 patients) suggests:

- Radiological response is significantly ↑ with combination chemotherapy ([39% vs 23% (OR 2.30 (95% CI 1.94 - 2.72)])
- There is a modest but statistically significant benefit in median OS for combination therapy
- Treatment related death ↑ with combination chemotherapy ([1.1% vs. 0.5% (OR 1.64, 95% CI 0.83 to 3.24)])

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>mOS (m) pre 2000</th>
<th>mOS (m) post 2000</th>
<th>p. value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Combination chemotherapy</td>
<td>4447</td>
<td>7.3</td>
<td>11.6</td>
<td>HR 0.84 (0.79 to 0.89)</td>
</tr>
<tr>
<td>Single drug chemotherapy</td>
<td>6.4</td>
<td>10.5</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
CHEMOTHERAPY FOR METASTATIC GASTRIC CANCER

Developments over time

FAMTX > BSC

ORR Cis-5FU > 5FU/5FU+ADM+MMC

ECF > FAMTX

FEMTX > BSC

DCF > CF


FAMTX, 5-FU doxorubicin, and methotrexate. FEMTX, 5-FU eprubicin, and methotrexate, ECF, etoposide, leucovorin, 5FU ECF, eprubicin, cisplatin, 5FU. ADM, adriamycin. MMC, mitomycin C
CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER
Doublet vs triplet chemotherapy

V325 Trial

Treatment naïve advanced gastric cancer

DCF (n=221)

CF (n=224)

Primary endpoint TTP

Radiological response rate DCF 37% vs 25% CF (p=0.01)

Addition of docetaxel to cisplatin and 5FU significantly improved overall survival

DCF Docetaxel 75 mg/m², cisplatin 75mg/m² D1, 5FU 750 mg/m²/d D1-5 q3W
CF, cisplatin 100mg/m² D1, 5FU 1000mg/m²/d D1-5 q3W


DCF
Cisplatin
5FU

Radiological response rate DCF 37% vs 25% CF (p=0.01)

HR 1.29; (95% CI, 1.0 to 1.6)
CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

Doublet vs triplet chemotherapy

TAX 325 Trial Toxicity

<table>
<thead>
<tr>
<th>Toxicity ≥ grade 3</th>
<th>DCF</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia ≥ grade 3</td>
<td>82%</td>
<td>57%</td>
</tr>
<tr>
<td>Febrile neutropenia</td>
<td>29%</td>
<td>12%</td>
</tr>
<tr>
<td>Death on treatment</td>
<td>3.6%</td>
<td>5.4%</td>
</tr>
</tbody>
</table>

In DCF arm complicated neutropenia with G-CSF was 12%

Addition of docetaxel to CF ↑ myelosupression and infection, but maintains QoL

DCF Docetaxel 75 mg/m², cisplatin 75mg/m² D1, 5FU 750 mg/m²/d D1-5 q3W
CF, cisplatin 100mg/m² D1, 5FU 1000mg/m²/d D1-5 q3W

CHEMOTHERAPY FOR METASTATIC GASTRIC CANCER

Modifications to docetaxel triplets

MODIFICATIONS TO DOCETAXEL TRIPLETS

<table>
<thead>
<tr>
<th>Docetaxel triplet</th>
<th>n</th>
<th>ORR</th>
<th>PFS(m)</th>
<th>OS (m)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastro-Tax-1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 40 mg/m², cisplatin 40 mg/m², leucovorin 200 mg/m² and 5FU 2000 mg/m² weekly</td>
<td>36 (M1)</td>
<td>47%</td>
<td>8.1</td>
<td>15.1</td>
</tr>
<tr>
<td><strong>FLOT</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 50 mg/m², oxaliplatin 85 mg/m² D1, leucovorin 200 mg/m² and 5FU 2600 mg/m² x24h Q2W</td>
<td>59</td>
<td>58%</td>
<td>5.2</td>
<td>11.1</td>
</tr>
<tr>
<td><strong>mDCF (US)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 40 mg/m² D1, cisplatin 40 mg/m² ID3, 5FU 2,000 mg/m² Q2W</td>
<td>54</td>
<td>49%</td>
<td>9.7</td>
<td>18.8</td>
</tr>
<tr>
<td><strong>TEX</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 50mg/m² D1, oxaliplatin 100mg/m² D1, capecitabine 625mg/m² bd po D1-21 Q3W</td>
<td>86</td>
<td>26%</td>
<td>5.5</td>
<td>11.3</td>
</tr>
<tr>
<td><strong>TEF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Docetaxel 50mg/m² D1, oxaliplatin 85mg/m² D1, 5FU 2400mg/m² x46h, folinic acid 400mg/m² D1-2 Q2W</td>
<td>89</td>
<td>47%</td>
<td>7.7</td>
<td>14.6</td>
</tr>
</tbody>
</table>

Docetaxel-triplets are associated with high response rates and encouraging survival (phase II caveat)

MODIFICATIONS TO DOCETAXEL TRIPELTS TOXICITY

<table>
<thead>
<tr>
<th>Docetaxel triplet</th>
<th>n</th>
<th>ORR (%)</th>
<th>PFS(m)</th>
<th>OS (m)</th>
<th>% G3+ neutropenia</th>
<th>% Febrile neutropenia</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Gastro-Tax-1</strong>[^1]</td>
<td>36 (M1)</td>
<td>47%</td>
<td>8.1</td>
<td>15.1</td>
<td>22</td>
<td>5</td>
</tr>
<tr>
<td>Docetaxel 40 mg/m², cisplatin 40 mg/m², leucovorin 200 mg/m² and 5FU 2000 mg/m² weekly</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>FLOT</strong>[^2]</td>
<td>59</td>
<td>58</td>
<td>5.2</td>
<td>11.1</td>
<td>48</td>
<td>3.8</td>
</tr>
<tr>
<td>Docetaxel 50 mg/m², oxaliplatin 85 mg/m² D1, leucovorin 200 mg/m² and 5FU 2600 mg/m² x24h Q2W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>mDCF (US)</strong>[^3]</td>
<td>54</td>
<td>49%</td>
<td>9.7</td>
<td>18.8</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>Docetaxel 40 mg/m² D1, cisplatin 40 mg/m² ID3, 5FU 2,000 mg/m² Q2W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TEX</strong>[^4]</td>
<td>86</td>
<td>26%</td>
<td>5.5</td>
<td>11.3</td>
<td>64</td>
<td>9</td>
</tr>
<tr>
<td>Docetaxel 50mg/m² D1, oxaliplatin 100mg/m² D1, capecitabine 625mg/m² bd po D1-21 Q3W</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>TEF</strong>[^4]</td>
<td>89</td>
<td>47%</td>
<td>7.7</td>
<td>14.6</td>
<td>56</td>
<td>2</td>
</tr>
<tr>
<td>Docetaxel 50mg/m² D1, oxaliplatin 85mg/m² D1, 5FU 2400mg/m² x46h, folic acid 400mg/m² D1-2 Q2W</td>
<td></td>
<td></td>
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<td></td>
</tr>
</tbody>
</table>

Modified docetaxel triplets still associated high levels myelotoxicity

CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

Doublet vs triplet chemotherapy

mDCF vs CF in Chinese patients

Treatment naïve advanced gastric cancer

DCF (n=121)

CF (n=122)

Primary endpoint PFS

Addition of docetaxel to CF increased RR, PFS and OS

DCF Docetaxel 60 mg/m², cisplatin 60mg/m² D1, 5FU 600 mg/m²/d D1-5 q3W
CF, cisplatin 75mg/m² D1, 5FU 600mg/m²/d D1-5 q3W

Toxicity ≥ grade 3

<table>
<thead>
<tr>
<th></th>
<th>DCF</th>
<th>CF</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutopenia ≥ grade 3</td>
<td>60.5%</td>
<td>9.6%</td>
</tr>
<tr>
<td>Febrile neutopenia</td>
<td>12.6%</td>
<td>0%</td>
</tr>
</tbody>
</table>

OXALIPLATIN OR CISPLATIN IN ADVANCED GASTRIC CANCER

REAL2 trial

Non-inferiority trial

Treatment naïve advanced gastric cancer

Oxaliplatin EOF or EOX (n=474)

Cisplatin ECF or ECX (n=490)

Toxicity G3+

<table>
<thead>
<tr>
<th></th>
<th>Oxaliplatin more common</th>
<th>Cisplatin more common</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhoea (11% vs 4%)</td>
<td>Neutropenia (45% vs 28%)</td>
<td></td>
</tr>
<tr>
<td>Neuropathy (6% vs 2%)</td>
<td>Thromboembolism (15% vs 7%)</td>
<td></td>
</tr>
</tbody>
</table>

HR for OS 0.92 (95% CI, 0.80 -1.10)

E= epirubicin 50mg/m^2, C=cisplatin 60mg/m^2 D1, O=oxaliplatin 130mg/m^2 D1
F=5FU 200mg/m^2 iv D1-21, X=capecitabine 650mg/m^2 D1-21

OXALIPLATIN OR CISPLATIN IN ADVANCED GASTRIC CANCER

FLO vs FLP

Treatment naïve advanced gastric cancer

Primary endpoint PFS

<table>
<thead>
<tr>
<th></th>
<th>FLO (n=112)</th>
<th>FLP (n=108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PFS &gt;65y</td>
<td>Median (months)</td>
<td>6.0</td>
</tr>
<tr>
<td>PFS ITT</td>
<td>Median (months)</td>
<td>5.8</td>
</tr>
<tr>
<td>OS &gt;65y</td>
<td>Median (months)</td>
<td>13.9</td>
</tr>
<tr>
<td>OS ITT</td>
<td>Median (months)</td>
<td>10.7</td>
</tr>
</tbody>
</table>

Toxicity ≥ grade 3

<table>
<thead>
<tr>
<th></th>
<th>FLO</th>
<th>FLP</th>
</tr>
</thead>
<tbody>
<tr>
<td>Neutropenia ≥ grade 3</td>
<td>11.6%</td>
<td>14.7%</td>
</tr>
<tr>
<td>SAR</td>
<td>9%</td>
<td>19%</td>
</tr>
</tbody>
</table>

FLO, oxaliplatin 85 mg/m², LV 200 mg/m², 5FU 2,600 mg/m² 24h iv Q2W
FLP, cisplatin 50 mg/m² Q2W, LV 200 mg/m², 5FU 2,000 mg/m² 24h iv Q7D 6 weeks on 2 weeks off

OXALIPLATIN VS CISPLATIN META-ANALYSIS

Contains four more recent cisplatin vs oxaliplatin studies but not REAL-2

Cochrane meta-analysis suggests a statistically significant benefit of oxaliplatin therapy versus cisplatin HR 0.81 (95% CI 0.67-0.98), pooled median OS was 14.0 months versus 11.3 months, respectively.

Results also favoured of oxaliplatin in terms of response rate and treatment related deaths

CAPECITABINE OR 5FU IN ADVANCED GASTRIC CANCER

REAL2 trial

Non-inferiority trial

Treatment naïve advanced gastric cancer

- Capecitabine EOX or ECX (n=480)
- 5FU EOF or ECF (n=484)

Toxicity

- Capecitabine more common
- Hand foot syndrome (43% vs 30% any grade)

HR for OS 0.86 (95% CI, 0.80 -0.99)

E= epirubicin 50mg/m², C= cisplatin 60mg/m² D1, O= oxaliplatin 130mg/m2 D1
F= 5FU 200mg/m² iv D1-21, X= capecitabine  650mg/m² D1-21

CAPECITABINE VS. 5FU META-ANALYSIS
Contains four more recent capecitabine vs 5FU studies but not REAL-2

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>S-1 N</th>
<th>5-FU N</th>
<th>log [Hazard Ratio] (SE)</th>
<th>Hazard Ratio IV,Fixed,95% CI</th>
<th>Weight</th>
<th>Hazard Ratio IV,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ajani 2010</td>
<td>521</td>
<td>508</td>
<td>-0.065 (0.088)</td>
<td></td>
<td>50.7%</td>
<td>0.92 [0.80, 1.05]</td>
</tr>
<tr>
<td>Boku 2009</td>
<td>234</td>
<td>234</td>
<td>-0.167 (0.095)</td>
<td></td>
<td>25.0%</td>
<td>0.83 [0.69, 1.00]</td>
</tr>
<tr>
<td>Chen 2015</td>
<td>30</td>
<td>30</td>
<td>-0.026 (0.116)</td>
<td></td>
<td>17.4%</td>
<td>0.97 [0.78, 1.22]</td>
</tr>
<tr>
<td>Li 2015</td>
<td>130</td>
<td>116</td>
<td>0.045 (0.196)</td>
<td></td>
<td>6.0%</td>
<td>1.05 [0.71, 1.54]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>905</td>
<td>888</td>
<td></td>
<td></td>
<td>100.0%</td>
<td>0.91 [0.83, 1.00]</td>
</tr>
</tbody>
</table>

Cochrane meta-analysis suggests a non-statistically significant benefit of capecitabine vs infusional 5FU 0.94 (95% CI 0.79 to 1.11), pooled median OS was 10.8 vs. 10.9 months, respectively.

The non-Asian trial of cisplatin-5FU vs cisplatin-S1 (FLAGS) was negative for an improvement in OS with S1 compared to 5FU, however a post hoc non-inferiority analysis suggested S1 was not inferior.\textsuperscript{1,2}

Meta-analysis suggests a small survival advantage to S1 compared to infusional 5FU (0.91 (95% CI 0.83 to 1.00))\textsuperscript{3}
NON-PLATINUM OPTIONS

Irinotecan

V306 Trial

Treatment naïve advanced gastric cancer

Irinotecan 5FU (n=170)
Cisplatin 5FU (n=163)

Toxicity

Irinotecan/5FU vs Cisplatin/5FU

Toxic death (0.6% vs 3%)
Neutropenia (25% vs 52%)
G3+ stomatitis (2% vs 17%)
Diarrhoea (22% vs 17%)

TTF was longer for IF than CF 4 vs. 3.4m P = 0.018

Irinotecan 80mg/m², folinic acid 500 mg/m², 5-fluorouracil 5-FU 2000 mg/m² 22h, 6/7 weeks or CF: cisplatin 100 mg/m² 1-3 h, with 5-FU 1000 mg/m²/day D1-5 q4wks.

NON-PLATINUM OPTIONS

Irinotecan

French study

Treatment naïve advanced gastric cancer

FOLFIRI then ECX (n=207)

ECX*then FOLFIRI (n=209)

Response rates were similar 39.2% v 37.8% ECX vs FOLFIRI
39% FOLFIRI and 48% ECX received 2nd line chemotherapy
More patients stopped ECX for toxicity than FOLFIRI
High grade haematological toxicity was more common with ECX

OS and PFS were not different between groups


Irinotecan 180mg/m², folinic acid 400 mg/m², 5-FU 2400 mg/m² in 46h Q2W
ECX, epirubicin 50mg/m², cisplatin, 60mg/m² capecitabine 1 g/m² bd D2:D15

TTF

5.1 v 4.2 months

HR, 0.77; 95% CI, 0.63 to 0.93; P = .008
CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER
Evidence based statements: first line chemotherapy

Chemotherapy improves survival and QoL compared to best supportive care.

Combination chemotherapy improves response rates and overall survival compared to single agent chemotherapy. Triplet chemotherapy is associated with ↑ORR and overall survival, but also ↑ toxicity.

Oxaliplatin and cisplatin are equivalent in a large non-inferiority study, however meta-analysis favours oxaliplatin in terms of OS, response rate and treatment related death.

Capecitabine and infusional 5FU (and possibly S1) are equivalent, with differing toxicity spectra.

Irinotecan has not demonstrated superiority or non-inferiority to platinum in terms of overall survival, but is associated with less toxicity and reduced TTF in two studies.
OVERALL SURVIVAL IN RANDOMISED TRIALS WITH CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

No improvement since 2008
Clinical trials are important.

SECOND LINE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER
2ND LINE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

AIO study

Previously treated advanced gastric cancer

- Irinotecan (n=21)
- BSC (n=19)

Response rate with irinotecan – 0%
Improvement of symptoms in 50% symptomatic patients

Irinotecan 250mg/m² Q3W C1, 350mg/m² cycle 2 onwards if tolerated

2ND LINE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

COUGAR-02

Previously treated advanced gastric cancer

Docetaxel (n=84)

BSC (n=84)

Response rate with docetaxel 7%
Toxicity associated with docetaxel
≥ G3 Neutropenia 15%
≥ G3 Febrile neutropenia 7%

Median OS 5.2m docetaxel vs 3.6m BSC

Docetaxel 75mg/m2 Q3W

2ND LINE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

Korean study

- Previously treated advanced gastric cancer (n=133)
  - Docetaxel or irinotecan
  - BSC (n=69)

Response rate with docetaxel 17%
Response rate with irinotecan 10%
≥ G3 Neutropenia 7%

Median OS 3.8m vs 5.3m
HR 0.657; 95% CI 0.49 0.89; P = .007

Docetaxel 60 mg/m² Q3W or irinotecan 150 mg/m² Q2W

**2\textsuperscript{ND} LINE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER**

**WG4007**

- **Previously treated advanced gastric cancer**
  - **Paclitaxel** (n=108)
  - **Irinotecan** (n=111)

**ORR** was 20.9% paclitaxel vs 13.6% in irinotecan (P = .24)

3\textsuperscript{rd} line treatment in 89.8% after paclitaxel treatment, 72.1% after irinotecan (P = .001).

Paclitaxel 80 mg/m\textsuperscript{2} on D1, D8, D15 Q4W, or irinotecan 150 mg/m\textsuperscript{2} Q2W.

- mOS 9.5m paclitaxel vs 8.4m irinotecan
  - HR 1.13; (95% CI, 0.86 - 1.49); P = 0.38

2ND LINE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

OS benefits are consistent across datasets

- **Docetaxel**
- **BSC**
- **Docetaxel/Irinotecan**
- **BSC**
- **Irinotecan**
- **BSC**

META-ANALYSIS 2ND LINE CHEMOTHERAPY GASTRIC CANCER

2nd line chemo vs none

Irinotecan vs docetaxel

Progression within 3–6m after prior chemotherapy (HR=0.39, 95% CI=0.26–0.59, P<0.0001)

Progression < 3m of completing treatment (HR=0.70, 95% CI=0.49–0.99, P=0.04)

Progression during treatment (HR=0.75, 95% CI=0.54–1.04, P=0.08).

**2ND LINE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER**

Benefit is greatest in ECOG 0 patients with sustained response to 1st line therapy

<table>
<thead>
<tr>
<th>ECOG PS</th>
<th>Events/patients</th>
<th>Docetaxel events</th>
<th>Hazard ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>Docetaxel</td>
<td>ASC</td>
<td></td>
</tr>
<tr>
<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>0.80 (0.53-1.21)</td>
</tr>
<tr>
<td>2</td>
<td>13/14 (92.9%)</td>
<td>12/12 (100%)</td>
<td>0.81 (0.35-1.82)</td>
</tr>
<tr>
<td>Stratified</td>
<td>80/84 (95.2%)</td>
<td>81/84 (96.4%)</td>
<td>0.72 (0.52-0.99)</td>
</tr>
</tbody>
</table>

Heterogeneity between groups χ²=1.7, p=0.43

<table>
<thead>
<tr>
<th>Progression</th>
<th>Events/patients</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>34/35 (94.4%)</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>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>0.33 (0.47-0.65)</td>
</tr>
<tr>
<td>Stratified</td>
<td>80/84 (95.2%)</td>
<td>81/84 (96.4%)</td>
<td>0.66 (0.47-0.91)</td>
</tr>
</tbody>
</table>

Heterogeneity between groups χ²=5.3, p=0.07

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

Heterogeneity between groups χ²=0.01, p=0.01

2\textsuperscript{ND} LINE CHEMOTHERAPY FOR ADVANCED GASTRIC CANCER

Evidence based statements

Second line chemotherapy provides a \textit{modest survival benefit} in advanced gastric cancer that has progressed following first line treatment.

\textbf{Paclitaxel, docetaxel and irinotecan} are all appropriate options.

Consideration of the risk;benefit ratio and patient quality of life is important in view of the limited benefit of treatment in this setting.