Neo-adjuvant and adjuvant treatment in gastric and GE junction cancer

Dr Ian Chau
Consultant Medical Oncologist
The Royal Marsden Hospital
London & Surrey
Disclosure

• Advisory Board: Sanofi Oncology, Eli-Lilly, Bristol Meyers Squibb, MSD, Bayer, Roche, Five Prime Therapeutics

• Research funding: Eli-Lilly, Janssen-Cilag, Sanofi Oncology, Merck-Serono, Novartis

• Honorarium: Taiho, Pfizer, Amgen, Eli-Lilly
Multimodality treatment of OGI/ gastric adenocarcinoma

Pre-operative
- Pre-operative chemoradiation
- Pre-operative chemotherapy
- Pre-operative chemotherapy

Post-operative
- Surgery
- Post-operative chemotherapy
- Surgery
- Post-operative chemotherapy
- Surgery
- Post-operative Chemoradiation
Multimodality treatment of OGI/ gastric adenocarcinoma

Pre-operative

Post-operative

Surgery

Post-operative chemotherapy
The GASTRIC Group meta-analysis

The GASTRIC (Global Advanced/Adjuvant Stomach Tumour Research International Collaboration) Group JAMA 2010

Probability of OS

Log-rank p<0.001

Time from randomisation (years)

5-year OS

Any chemotherapy

Surgery alone

No. at risk

Any chemotherapy 1,924 1,688 1,385 1,217 1080 929 709 526 390 297 243

Surgery alone 1,857 1,568 1,300 1,092 952 782 583 407 267 172 138

The GASTRIC (Global Advanced/Adjuvant Stomach Tumour Research International Collaboration) Group JAMA 2010
The GASTRIC Group meta-analysis (cont’d)

<table>
<thead>
<tr>
<th>Events/patients</th>
<th>Statistics</th>
<th>Any CT</th>
<th>Surgery alone</th>
<th>(O-E)</th>
<th>Var.</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Loc: Europe</strong></td>
<td></td>
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<tr>
<td>Coombes et al, 1990</td>
<td></td>
<td>86/133</td>
<td>102/148</td>
<td>-7.8</td>
<td>46.7</td>
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<tr>
<td>Grau et al, 1993</td>
<td></td>
<td>42/64</td>
<td>49/63</td>
<td>-9.4</td>
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<td>Lise et al, 1995</td>
<td></td>
<td>88/152</td>
<td>99/154</td>
<td>-7.5</td>
<td>46.6</td>
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<td>Tryavaris et al, 1996</td>
<td></td>
<td>25/44</td>
<td>38/43</td>
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<tr>
<td>Bajetta et al, 2002</td>
<td></td>
<td>67/135</td>
<td>69/136</td>
<td>-0.7</td>
<td>34</td>
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<tr>
<td>Popiela et al, 2004</td>
<td></td>
<td>42/53</td>
<td>47/52</td>
<td>-8</td>
<td>20.2</td>
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<tr>
<td>Bouche et al, 2005</td>
<td></td>
<td>79/133</td>
<td>90/138</td>
<td>-8.2</td>
<td>42.1</td>
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<td>Nitti et al, 2006a</td>
<td></td>
<td>50/103</td>
<td>55/103</td>
<td>-3.3</td>
<td>26.2</td>
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<tr>
<td>Nitti et al, 2006b</td>
<td></td>
<td>63/89</td>
<td>64/97</td>
<td>1.6</td>
<td>31.6</td>
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<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td>542/906</td>
<td>613/934</td>
<td>-52</td>
<td>284.8</td>
</tr>
<tr>
<td>Heterogeneity Chi-square=7.18, df=8: p&gt;0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Loc: USA</strong></td>
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<td></td>
<td></td>
<td></td>
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<tr>
<td>Douglass et al, 1982</td>
<td></td>
<td>64/88</td>
<td>73/82</td>
<td>-13.7</td>
<td>33</td>
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<tr>
<td>Engstrom et al, 1985</td>
<td></td>
<td>73/91</td>
<td>72/89</td>
<td>-2.3</td>
<td>36</td>
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<tr>
<td>Krook et al, 1991</td>
<td></td>
<td>51/63</td>
<td>50/64</td>
<td>0.9</td>
<td>25.1</td>
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<tr>
<td>MacDonald et al, 1995</td>
<td></td>
<td>90/109</td>
<td>96/112</td>
<td>-2.7</td>
<td>46.4</td>
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<tr>
<td><strong>Subtotal</strong></td>
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<td>278/351</td>
<td>291/347</td>
<td>-17.8</td>
<td>140.4</td>
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<td>Heterogeneity Chi-square=3.81, df=3: p&gt;0.1</td>
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<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td><strong>Loc: Asia</strong></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Nakajima et al, 1984</td>
<td></td>
<td>102/156</td>
<td>52/72</td>
<td>-8.3</td>
<td>31.1</td>
</tr>
<tr>
<td>Nakajima et al, 1999</td>
<td></td>
<td>47/288</td>
<td>60/25</td>
<td>-7</td>
<td>26.7</td>
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<tr>
<td>Nashimoto et al, 2003</td>
<td></td>
<td>13/128</td>
<td>21/124</td>
<td>-4.3</td>
<td>8.5</td>
</tr>
<tr>
<td>Nakajima et al, 2007</td>
<td></td>
<td>18/95</td>
<td>30/95</td>
<td>-7.9</td>
<td>11.7</td>
</tr>
<tr>
<td><strong>Subtotal</strong></td>
<td></td>
<td>180/667</td>
<td>163/576</td>
<td>-27.5</td>
<td>78.1</td>
</tr>
<tr>
<td>Heterogeneity Chi-square=1.86, df=3: p&gt;0.1</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td></td>
<td>1000/1924</td>
<td>1067/1857</td>
<td>-97.4</td>
<td>503.3</td>
</tr>
</tbody>
</table>

No significant heterogeneity was detected across the three continents (p=0.27) 0.83 (0.74-0.94)

The GASTRIC Group JAMA 2010
Adjuvant therapy in gastric cancer

ACTS-GC\textsuperscript{1}

n=529

S-1

Observation

n=530

CLASSIC\textsuperscript{2}

n=520

CAPOX

Observation

n=515

HR: 0.66; 95% CI: 0.51-0.85
p=0.0015

\textsuperscript{1}Sasako et al. J Clin Oncol 2011; \textsuperscript{2}Noh et al Lancet Oncol 2014
HR: 0.98; 95% CI: 0.82-1.18;  
p=0.865  
5-yr OS: 51% for sequential arm  
50.6% for 5FU/LV arm  
Bajetta et al Ann Oncol 2014
# AJCC pathological stage at randomisation

<table>
<thead>
<tr>
<th></th>
<th>CLASSIC(^1)</th>
<th>ITACA-S(^2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>1,035</td>
<td>1,100</td>
</tr>
<tr>
<td>II</td>
<td>50%</td>
<td>31.8%</td>
</tr>
<tr>
<td>IIIA</td>
<td>36%</td>
<td>27.3%</td>
</tr>
<tr>
<td>IIIB</td>
<td>13%</td>
<td>14.4%</td>
</tr>
<tr>
<td>IV</td>
<td>&lt;1%</td>
<td>18.3%</td>
</tr>
</tbody>
</table>

\(^1\)Bang et al Lancet 2012; \(^2\)Bajetta et al Ann Oncol 2014
SAMIT trial design

- Primary endpoint: DFS
- 2×2 factorial design
- To show superiority of paclitaxel + oral fluoropyrimidines over fluoropyrimidines alone
- To show non-inferiority of S-1 to UFT

Tsuburaya et al Lancet Oncol 2014
SAMIT: DFS outcome

Monotherapy vs. Sequential treatment

UFT vs. S-1

HR: 0.92; 95% CI: 0.80-1.07;  
HR: 0.81; 95% CI: 0.70-0.93;

p=0.273  
p=0.0048  

Sequential Mono

3-yr DFS: 57.2% 54.0%  
3-yr OS: 59.3% 55.8%  

3-yr DFS: 53.0% 58.2%  
3-yr OS: 54.3% 60.7%  

Tsuburaya et al Lancet Oncol 2014
Multimodality treatment of OGI/ gastric adenocarcinoma

Pre-operative

Post-operative

Surgery

Post-operative chemoradiation
Post-operative chemoradiation in resected OGJ/gastric cancer

Intergroup 0116\textsuperscript{1}

<table>
<thead>
<tr>
<th>Treatment</th>
<th>n</th>
<th>Events</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU + leucovorin + RT</td>
<td>282</td>
<td>209</td>
<td>35</td>
</tr>
<tr>
<td>Observation</td>
<td>277</td>
<td>229</td>
<td>27</td>
</tr>
</tbody>
</table>

\( P = .0046 \)

CALGB 80101\textsuperscript{2}

\begin{align*}
\text{ECF} & \quad \text{5FU} \\
\text{Probability} & \quad \text{Probability} \\
0 & \quad 0 \\
0.2 & \quad 0.2 \\
0.4 & \quad 0.4 \\
0.6 & \quad 0.6 \\
0.8 & \quad 0.8 \\
1.0 & \quad 1.0 \\
\end{align*}

\( P \) years from study entry

\textsuperscript{1}Smalley et al J Clin Oncol 2012; \textsuperscript{2}Fuchs et al ASCO 2011
Multimodality treatment of OGI/ gastric adenocarcinoma

Pre-operative

Post-operative

Surgery

Post-operative chemotheraphy

Surgery

Post-operative Chemoradiation
ARTIST: trial design

D2 resected gastric cancer

• Primary outcome: DFS
• Secondary endpoints: overall survival, recurrence rate, safety

n= 228

R

XP

Cisplatin 60mg/m²
Capecitabine 2,000mg/m²/day for 14 days
q 3 weeks for 6 cycles

n= 230

XP × 2 cycles

Capecitabine 1650mg/m²/d + RT 45Gy for 5 weeks

XP × 2 cycles

Lee et al J Clin Oncol 2012; Park et al J Clin Oncol 2015
ARTIST: survival outcome

Disease free survival

Overall survival

5 year OS
XPRT 75%
XP 73%

Park et al J Clin Oncol 2015
Chinese RCT trial design

- Primary outcome: OS
- Secondary endpoints: recurrence free survival, recurrence rate, toxicity

D2 resected gastric cancer

- n=175
  - 5-FU/LV
  - 5-FU 400mg/m² LV 20mg/m² daily for 5 days q 4 weeks for 4 cycles

- n=205
  - 5-FU/LV × 1 cycles
  - 5-FU/LV + IMRT 45Gy for 5 weeks × 2 cycles

Zhu et al Radiother Oncol 2012
Survival outcomes

Overall survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-year OS</th>
<th>Median OS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo alone</td>
<td>41.8%</td>
<td>38 months</td>
</tr>
<tr>
<td>IMRT-C</td>
<td>48.4%</td>
<td>54 months</td>
</tr>
</tbody>
</table>

HR: 1.24; 95% CI: 0.94, 1.65; p=0.122

Recurrence free survival

<table>
<thead>
<tr>
<th>Treatment</th>
<th>5-year RFS</th>
<th>Median RFS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chemo alone</td>
<td>35.8%</td>
<td>32 months</td>
</tr>
<tr>
<td>IMRT-C</td>
<td>45.2%</td>
<td>50 months</td>
</tr>
</tbody>
</table>

HR: 1.35; 95% CI: 1.03, 1.78; p=0.029

Zhu et al Radiother Oncol 2012
Multimodality treatment of OGI/ gastric adenocarcinoma

Pre-operative

- Pre-operative chemoradiation
  - Surgery

Post-operative
CROSS Pre-op CRT

Paclitaxel/carboplatin + RT

Surgery

Patients with carcinoma of oesophagus and OGJ
24% OGJ tumours
75% adeno

n=178

n=188

Shapiro et al Lancet Oncol 2015
Multimodality treatment of OGJ/ gastric adenocarcinoma

Pre-operative

Pre-operative chemotherapy

Surgery

Post-operative chemotherapy

Post-operative
# Neoadjuvant vs adjuvant chemotherapy in resectable gastric cancer (SAKK 43/99)

Patients with resectable cancer of stomach

<table>
<thead>
<tr>
<th></th>
<th>Neoadjuvant</th>
<th>Adjuvant</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underwent surgery</td>
<td>94%</td>
<td>100%</td>
</tr>
<tr>
<td>R0 resection</td>
<td>85%</td>
<td>91%</td>
</tr>
<tr>
<td>Completed planned 4 cycles</td>
<td>74%</td>
<td>34%</td>
</tr>
<tr>
<td>Serious adverse events</td>
<td>11%</td>
<td>23%</td>
</tr>
<tr>
<td>pCR</td>
<td>11.7%</td>
<td>-</td>
</tr>
</tbody>
</table>

Biffi et al. World J Gastroenterol 2010
SAKK43/99 trial 10-year survival outcome

Event free survival

Overall survival

5-year EFS: 44.1% Neoadjuvant 44.1% Adjuvant 43.5%
10-year EFS: 44.1% 29.4%
5-year OS: 47% 46%
10-year OS: 44% 36% Fazio et al Ann Oncol 2016
Peri-operative chemotherapy

**MAGIC**

- **HR** = 0.75; 95% CI: 0.60–0.93
- **p** = 0.009

- **CSC** = peri-operative ECF; **S** = surgery alone

**FNLCC ACCORD 07-FFCD 9703 trial**

- Log-rank **p** = 0.02
- **HR** = 0.69 (95% CI, 0.50 to 0.95)

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ST03 trial design

- Primary endpoint: OS
- Target recruitment: 1,100 patients (80% power to detect 10% increase in 5-year survival from 40% to 50%)

ECX = epirubicin, cisplatin, capecitabine

Cunningham et al Lancet Oncology 2017
STO3 survival

- **508 deaths** (248 ECX, 260 ECX+B) have been observed
  - Median follow-up is 33 months in both arms

<table>
<thead>
<tr>
<th>Overall survival</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Median OS</strong></td>
</tr>
<tr>
<td>ECX</td>
</tr>
<tr>
<td>ECX+B</td>
</tr>
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</table>

<table>
<thead>
<tr>
<th>Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>(95% CI)</strong></td>
</tr>
<tr>
<td>HR=1.09</td>
</tr>
<tr>
<td>(0.91 to 1.29)</td>
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</table>

<table>
<thead>
<tr>
<th>Log-rank p-value</th>
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<tbody>
<tr>
<td>0.36</td>
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<table>
<thead>
<tr>
<th>3-year overall survival (95% CI)</th>
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<tbody>
<tr>
<td><strong>ECX</strong></td>
</tr>
<tr>
<td>50.3% (45.5% to 54.9%)</td>
</tr>
<tr>
<td><strong>ECX+B</strong></td>
</tr>
<tr>
<td>48.1% (43.2% to 52.7%)</td>
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</table>

<table>
<thead>
<tr>
<th>Secondary outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PFS</strong></td>
</tr>
<tr>
<td>HR=1.05 p=0.56</td>
</tr>
<tr>
<td><strong>DFS</strong></td>
</tr>
<tr>
<td>HR=1.04 p=0.62</td>
</tr>
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</table>

Cunningham et al Lancet Oncology 2017
Survival vs. MAGIC

Overall survival in ST03 compared with chemotherapy plus surgery (CSC) arm in MAGIC

Cunningham et al ECC 2015
Patients with T2-4, any N, M0 or every T, N+, M0 adenocarcinoma of OGJ and stomach

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

ECC/F = epirubicin, cisplatin, capecitabine/ 5-FU every 3 weeks
FLOT = Docetaxel, oxaliplatin, 5-FU every 2 weeks

Al-Batran et al Lancet Oncol 2016; ASCO 2017
FLOT4: Progression-Free Survival

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPFS</td>
<td>18 months</td>
<td>30 months</td>
</tr>
<tr>
<td></td>
<td>[15-22]</td>
<td>[21-41]</td>
</tr>
<tr>
<td>HR</td>
<td>0.75 [0.62-0.91]</td>
<td>p=0.004 (log rank)</td>
</tr>
<tr>
<td>PFS rate*</td>
<td>ECF/ECX</td>
<td>FLOT</td>
</tr>
<tr>
<td>2y</td>
<td>43%</td>
<td>53%</td>
</tr>
<tr>
<td>3y</td>
<td>37%</td>
<td>46%</td>
</tr>
<tr>
<td>5y*</td>
<td>31%</td>
<td>41%</td>
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</tbody>
</table>

*projected PFS rates

Al-Batran et al ASCO 2017
FLOT4: Overall Survival

![Graph showing overall survival over time with comparison between ECF/ECX and FLOT treatments.](image)

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX</th>
<th>FLOT</th>
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<tbody>
<tr>
<td>mOS</td>
<td>35 months</td>
<td>50 months</td>
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<tr>
<td></td>
<td>[27-46]</td>
<td>[38-na]</td>
</tr>
<tr>
<td>HR</td>
<td>0.77 [0.63 - 0.94]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>p=0.012 (log rank)</td>
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</tbody>
</table>

**OS rate**

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>2y</td>
<td>59%</td>
<td>68%</td>
</tr>
<tr>
<td>3y</td>
<td>48%</td>
<td>57%</td>
</tr>
<tr>
<td>5y</td>
<td>36%</td>
<td>45%</td>
</tr>
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</table>

*projected OS rates

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Al-Batran et al ASCO 2017
## Chemo Related Toxicity

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX (N=354)</th>
<th>FLOT (N=354)</th>
<th>P-value (Chi-Square)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diarrhea</td>
<td>13 (4%)</td>
<td>34 (10%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Vomiting</td>
<td>27 (8%)</td>
<td>7 (2%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Nausea</td>
<td>55 (16%)</td>
<td>26 (7%)</td>
<td>0.001</td>
</tr>
<tr>
<td>Fatigue</td>
<td>38 (11%)</td>
<td>25 (7%)</td>
<td></td>
</tr>
<tr>
<td>Infections</td>
<td>30 (9%)</td>
<td>63 (18%)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>75 (21%)</td>
<td>94 (27%)</td>
<td></td>
</tr>
<tr>
<td>Neutropenia</td>
<td>139 (39%)</td>
<td>181 (51%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Sensory</td>
<td>7 (2%)</td>
<td>24 (7%)</td>
<td>0.002</td>
</tr>
<tr>
<td>Thromboembolic</td>
<td>22 (6%)</td>
<td>9 (3%)</td>
<td>0.03</td>
</tr>
<tr>
<td>Anemia</td>
<td>20 (6%)</td>
<td>9 (3%)</td>
<td>0.04</td>
</tr>
</tbody>
</table>

Al-Batran et al ASCO 2017
Multimodality treatment of OGJ/ gastric adenocarcinoma

Pre-operative
- Pre-operative chemotherapy
- Surgery
- Post-operative Chemoradiation

Post-operative
- Pre-operative chemotherapy
- Surgery
- Post-operative chemotherapy
CRITICS survival outcome

Patients with stage Ib-IVa adenocarcinoma of OGJ and stomach:
- n=393
- n=395

Overall survival

Post op CRT:
- RT 45Gy in 25#
- Cisplatin weekly
- Capecitabine daily

Verheij et al ASCO 2016
Can we predict better who is going to benefit from which (neo)adjuvant therapy?
THE ROYAL MARSDEN

MUNICON

T3 or T4 adenocarcinoma of type 1 and 2 OGJ
Received Cisplatin/5-FU ± paclitaxel
Oxaliplatin instead of cisplatin if GFR <60ml/kg/min

Metabolic responders
n=54
Chemotherapy for 12 weeks

PET Day 0
Chemotherapy
Platinum/5-FU± Paclitaxel

Metabolic response defined as:
↓ of ≥35% tumour glucose SUV
Primary endpoint: median overall survival

PET Day 14

Primary endpoint: median overall survival

Lordick et al Lancet Oncology 2007
Event-free and overall survival

Event free survival

Overall survival

Lordick et al Lancet Oncology 2007
MUNICON II

T3 or T4 adenocarcinoma of type 1 and 2 OGJ
Received Cisplatin/5-FU ± paclitaxel
Oxaliplatin instead of cisplatin if GFR <60ml/kg/min

Metabolic responders
n=33

Chemotherapy for 12 weeks

Surgery

Metabolic non-responders
n=23

ChemoRT C or F + 32Gy in 20#

PET Day 0

Chemotherapy
Platinum/5-FU ± Paclitaxel

Metabolic response defined as:
↓ of ≥35% tumour glucose SUV
Primary endpoint: R0 resection rate
Time to progression and overall survival

**Time to progression**

- **Estimated progression-free probability**
  - **PET responder**
  - **PET nonresponder**
  - *P = 0.035*

**Overall survival**

- **Estimated survival probability**
  - **PET responder**
  - **PET nonresponder**
  - *P = 0.10*

**Patients at risk**

<table>
<thead>
<tr>
<th></th>
<th>PET responder</th>
<th>PET nonresponder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Months since 2nd PET evaluation</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>33</td>
<td>23</td>
</tr>
<tr>
<td>6</td>
<td>28</td>
<td>17</td>
</tr>
<tr>
<td>12</td>
<td>23</td>
<td>13</td>
</tr>
<tr>
<td>18</td>
<td>19</td>
<td>10</td>
</tr>
<tr>
<td>24</td>
<td>12</td>
<td>5</td>
</tr>
<tr>
<td>30</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>36</td>
<td>10</td>
<td>3</td>
</tr>
<tr>
<td>42</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>48</td>
<td>2</td>
<td>0</td>
</tr>
</tbody>
</table>

Australisan AGITG DOCTOR randomised trial

T2 or more, T1N+ or poorly differentiated adenocarcinoma of oesophagus/OGJ (type 1 and II)

Received Pre-operative Cisplatin/5-FU

PET Day 0

Chemotherapy Cisplatin/5-FU

PET Day 15

Continue CF

Metabolic responders
n=45

Surgery

Metabolic non-responders
n=77

Primary endpoint: major histological response (<10% residual viable primary tumour) to the neoadjuvant therapy regimen

Barbour et al ESMO 2016
Australisan AGITG DOCTOR randomised trial

<table>
<thead>
<tr>
<th></th>
<th>Metabolic responder ((\downarrow\text{FDG uptake} &gt; 35%))</th>
<th>Metabolic non-responder ((\downarrow\text{FDG uptake} \leq 35%))</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>45</td>
<td>31</td>
</tr>
<tr>
<td>DCF</td>
<td>31</td>
<td>35</td>
</tr>
<tr>
<td>Primary endpoint</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major histopathological response</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;10% residual tumour</td>
<td>3/45 7%</td>
<td>6/31 19%</td>
</tr>
<tr>
<td>10-50% residual tumour</td>
<td>11%</td>
<td>21%</td>
</tr>
<tr>
<td>&gt;50% residual tumour</td>
<td>82%</td>
<td>58%</td>
</tr>
<tr>
<td>R0 resection</td>
<td>69%</td>
<td>64%</td>
</tr>
</tbody>
</table>

Barbour et al ESMO 2016
CALGB 80803 Trial Schema

T3/4 or N+ Esophageal/GEJ Adenoca PET Scan pre-treatment

PET Scan day 36-42

Induction Chemo: modified FOLFOX6 days 1,15, 29

PET responders: ≥ 35% decrease in SUV: continue initial chemo + concurrent RT (50.4 Gy in 28 fx)

Surgical resection 6 weeks post-RT

PET non-responders: < 35% decrease in SUV: cross-over to alternative chemo + concurrent RT (50.4 Gy in 28 fx)

Induction Chemo: Carboplatin/ Paclitaxel days 1,8,22,29

Companion Studies
- Quality of life
- Molecular markers of response

Goodman et al ASCO GI 2017
pCR Rates

**Induction**
- **mFOLFOX n=129**
  - **PET Responder** 73/129 (57%)
  - **Concurrent FOLFOX**
  - **Evaluable**
  - **pCR: 24/64 (37.5%)**
  - **PET Non-Responder** 39/129 (30%)
  - **Concurrent Carbo/Taxol**
  - **Evaluable**
  - **pCR: 7/37 (19.0%)**

**Induction**
- **Carbo/Taxol n=128**
  - **PET Responder** 64/128 (50%)
  - **Concurrent Carbo/Taxol**
  - **Evaluable**
  - **pCR: 7/56 (12.5%)**
  - **PET Non-Responder** 49/128 (38%)
  - **Concurrent FOLFOX**
  - **Evaluable**
  - **pCR: 7/41* (17.0%)**

---

**Efficacy criteria met for both induction arms**

*One ypT0N1 excluded*

Goodman et al ASCO GI 2017
PET metabolic response as biomarker for stratified management of oesophageal/OGJ cancer patients

Neoadjuvant chemotherapy

Control arm

Surgery

PET directed therapy

Good metabolic response

≥35% decrease in SUV

Surgery

Completion of post-op chemo

Poor metabolic response

<35% decrease in SUV

Alternative chemo

Alternative chemo + RT

??Deferral of surgery

??Deferral of surgery
pTRG and survival – MAGIC trial

TRG criteria: Mandard criteria

Survival by Mandard TRG (STO 3)

Based on assessment by local pathology departments

3 year survival (95% CI)

<table>
<thead>
<tr>
<th>Grade</th>
<th>Survival (%)</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>73.3%</td>
<td>(60.9% to 82.3%)</td>
</tr>
<tr>
<td>3</td>
<td>57.9%</td>
<td>(47.3% to 67.1%)</td>
</tr>
<tr>
<td>4-5</td>
<td>43.7%</td>
<td>(37.8% to 49.4%)</td>
</tr>
<tr>
<td>No resection</td>
<td>7.2%</td>
<td>(3.4% to 12.9%)</td>
</tr>
</tbody>
</table>

Hazard ratio (1-2 vs. others)

| Hazard ratio | 0.281 (0.189 to 0.418) | p < 0.0001 |

Cunningham et al ECC 2015
Experimental trial design for poor pathological response to neoadjuvant chemo in gastric cancer

Neoadjuvant platinum + fluoropyrimidine (XP, FOLFOX, FLOT) × 2-4 cycles → Surgery

One of the following pathology variables:
- ypT3-4
- ypN+
- R1
- ypTRG grades 4-5

Co-primary endpoint: overall survival
progression free survival
1:2:2 randomisation

R

N=120
Continue same chemo

N=240
Experimental drug X

N=240
Experimental Drug Y
THE ROYAL MARSDEN

THE ROYAL MARSDEN

Oncogenes
• Amplification – FISH/CISH
• Overexpression - IHC

Tumour suppressor genes
• Deletions – FISH
• Downregulation - IHC

Microdissection
• aCGH
• Expression profiling
• miRNA assays
• Methylation assays

Tissue Microarray (TMA)

Patient tumour sample
ECF/X vs. FLOT
Genomic subtype for gastric cancer

171 gene set identified 2 intrinsic subtypes:
Genomic intestinal (G-INT)
Genomic diffuse (G-DIF)

Tan et al Gastroenterology 2011
Differential effect to chemotherapy according to intrinsic subtype of gastric cancer

<table>
<thead>
<tr>
<th>Treatment</th>
<th>G-INT (deaths/n)</th>
<th>G-DIF (deaths/n)</th>
<th>HR (95% CI), P value (G-INT: HR = 1.0)</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjuvant 5-FU–based treatment</td>
<td>20/45 (44%)</td>
<td>29/38 (76%)</td>
<td>2.71 (1.52–4.85), P = .001</td>
<td>.002</td>
</tr>
<tr>
<td>Surgery alone</td>
<td>49/136 (36%)</td>
<td>48/86 (56%)</td>
<td>1.37 (0.92–2.05), P = .12</td>
<td></td>
</tr>
</tbody>
</table>

HR (95%CI), P value (5-FU–based therapy, HR = 1)

1.68 (0.98–2.88), P = .06
0.90 (0.56–1.45), P = .67

Tan et al Gastroenterology 2011
Microarray-based tumour molecular profiling to direct choice of platinum compounds: proof-of-concept phase II study

G1: oxaliplatin-sensitive
G2: cisplatin-sensitive
G3: status unclear or gene expression not available

Median turnaround time = 7 (IQR 5-9) working days
Microarray-based tumour molecular profiling to direct choice of platinum compounds: proof-of-concept phase II study

<table>
<thead>
<tr>
<th></th>
<th>G1 (Intestinal)</th>
<th>G2 (Diffuse)</th>
<th>G3 (Unknown)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SOX</td>
<td>SP</td>
<td>SP</td>
</tr>
<tr>
<td>n</td>
<td>30</td>
<td>13</td>
<td>19</td>
</tr>
<tr>
<td>PR</td>
<td>13 (44.8%)</td>
<td>1 (8.3%)</td>
<td>4 (26.7%)</td>
</tr>
<tr>
<td>SD</td>
<td>10 (34.5%)</td>
<td>10 (83.4%)</td>
<td>9 (60.0%)</td>
</tr>
<tr>
<td>PD</td>
<td>6 (20.7%)</td>
<td>1 (8.3%)</td>
<td>2 (13.3%)</td>
</tr>
<tr>
<td>NA</td>
<td>1</td>
<td>1</td>
<td>4</td>
</tr>
</tbody>
</table>

G1: oxaliplatin-sensitive
G2: cisplatin-sensitive
G3: status unclear or gene expression not available

Yong et al GI ASCO 2017
Genomic subtype for gastric cancer

3 intrinsic subtypes identified:
- Mesenchymal
- Proliferative
- Metabolic

Lei et al. Gastroenterology 2013
There is some evidence of an interaction between treatment arm and ERBB2 (p=0.027); reflecting very high survival rates amongst the small group of patients on the chemotherapy arm with ERBB2 overexpression.
Adjuvant S-1 in gastric cancer

(ACTS-GC)

Number of patients | HR (95% CI) | P value for interaction
--- | --- | ---
Sex
Female | 264 | 0.497 (0.316–0.782) | 0.208
Male | 565 | 0.709 (0.527–0.953)
Age
<60 y | 318 | 0.532 (0.351–0.806) | 0.140
60–69 y | 310 | 0.583 (0.374–0.908)
70–80 y | 201 | 0.816 (0.528–1.261)
Cancer stage (Japanese Classification)
II | 372 | 0.587 (0.377–0.913) | 0.551
IIa | 321 | 0.576 (0.394–0.841)
IIib | 136 | 0.745 (0.455–1.222)
Histologic type
Undifferentiated | 494 | 0.588 (0.422–0.819) | 0.442
Differentiated | 332 | 0.714 (0.492–1.038)
EGFR status
Negative | 754 | 0.625 (0.479–0.814) | 0.668
Positive | 75 | 0.745 (0.372–1.487)
HER2 status
Negative | 716 | 0.634 (0.485–0.830) | 0.998
Positive | 113 | 0.635 (0.337–1.196)

Terashima et al Clin Cancer Res 2012
Intergroup 0116 chemoradiation in resected gastric cancer

Gordon et al Ann Oncol 2013
ARTIST: HER 2 and other biomarkers correlation

<table>
<thead>
<tr>
<th></th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>0.740</td>
<td>0.520 to 1.050</td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>0.665</td>
<td>0.392 to 1.129</td>
</tr>
<tr>
<td>1</td>
<td>0.835</td>
<td>0.544 to 1.280</td>
</tr>
<tr>
<td>Gastrectomy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Subtotal</td>
<td>0.793</td>
<td>0.495 to 1.271</td>
</tr>
<tr>
<td>Total</td>
<td>0.701</td>
<td>0.438 to 1.121</td>
</tr>
<tr>
<td>LN</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>1.359</td>
<td>0.477 to 3.876</td>
</tr>
<tr>
<td>Positive</td>
<td>0.700</td>
<td>0.493 to 0.994</td>
</tr>
<tr>
<td>LN ratio</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 0.083</td>
<td>0.714</td>
<td>0.407 to 1.252</td>
</tr>
<tr>
<td>≥ 0.083</td>
<td>0.708</td>
<td>0.466 to 1.019</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>IB/II</td>
<td>0.676</td>
<td>0.387 to 1.181</td>
</tr>
<tr>
<td>III/IV (M0)</td>
<td>0.703</td>
<td>0.530 to 1.017</td>
</tr>
<tr>
<td>Intestinal</td>
<td>0.442</td>
<td>0.231 to 0.845</td>
</tr>
<tr>
<td>Diffuse</td>
<td>0.826</td>
<td>0.543 to 1.255</td>
</tr>
<tr>
<td>HER2</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2+</td>
<td>0.749</td>
<td>0.533 to 1.063</td>
</tr>
<tr>
<td>≥ 3</td>
<td>0.976</td>
<td>0.197 to 4.842</td>
</tr>
<tr>
<td>MET</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2+</td>
<td>0.749</td>
<td>0.534 to 1.050</td>
</tr>
<tr>
<td>≥ 3</td>
<td>1.414</td>
<td>0.196 to 10.197</td>
</tr>
<tr>
<td>MLH1</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>1.167</td>
<td>0.313 to 4.347</td>
</tr>
<tr>
<td>MLH1 loss</td>
<td>0.788</td>
<td>0.544 to 1.143</td>
</tr>
<tr>
<td>E-cadherin</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0.566</td>
<td>0.160 to 2.007</td>
</tr>
<tr>
<td>E-cadherin loss</td>
<td>0.859</td>
<td>0.591 to 1.247</td>
</tr>
</tbody>
</table>

Park et al J Clin Oncol 2015
Can treatment be tailored according to TCGA subtype?

EBV: 9%
MSI: 22%
GS: 20%
CIN: 50%

EBV-infected/MSI gastric cancer

PD-L1 expression

Interferon-\(\gamma\) gene set enrichment

TI: tumour-infiltrating
IM: invasive margin

120/1318 (9.1%) EBV-associated in resected gastric cancer specimens*

Derks et al Oncotarget 2016; *Kim et al ASCO 2017
Overall survival by microsatellite status - MAGIC

20/303 (6.7%) had MSI-H tumours

Smyth et al JAMA Oncol 2017
Overall survival by microsatellite status - CLASSIC

A. Among patients treated with surgery alone, those with microsatellite instability-high tumors had significantly better disease-free survival, compared to those with microsatellite-stable tumors (log-rank: p = 0.0149). B. Among those who received adjuvant chemotherapy, disease-free survival did not differ significantly with respect to the microsatellite instability status (log-rank: p = 0.1132). C. Among patients with microsatellite-stable disease, adjuvant chemotherapy provided a disease-free survival benefit over surgery alone (log-rank: p = 0.0025). D. However, among patients with microsatellite instability-high gastric cancer, disease-free survival did not differ significantly between those treated with adjuvant chemotherapy and those who underwent surgery alone (log-rank: p = 0.7858).

36/592 (6.1%) had MSI-H tumours

Kim et al ASCO 2017
Peri-operative immunotherapy

Pre-operative

Pre-operative chemoradiation

Surgery

Post-operative nivolumab

Post-operative

CHECKMATE 577

n=760

Screening

• Age ≥18 years
• Stage II/III carcinoma of the E/GEJ
• Completed pre-operative CRT followed by surgery
• Residual pathologic disease following complete resection

Treatment

Nivolumab

Placebo

Randomized

Post-treatment follow-up
Peri-operative immunotherapy

Pre-operative

- Pre-operative Chemo + PEMBRO
- Patients with resectable adenocarcinoma of OGI and stomach

Post-operative

- Post-operative chemo + PEMBRO

KEYNOTE 589

- CX x3 (FLOT ×4)
- n=800

Surgery

- CX x3 (FLOT ×4) + pembrolizumab

Pembro q3w x ~1 year
The Cancer Genome Atlas
oesophageal cancer

The Cancer Genome Atlas Research Network; Nature 2017
Multimodality treatment of OGJ/ gastric adenocarcinoma

Pre-operative
- Pre-operative chemoradiation
  - Surgery
- Pre-operative chemotherapy
  - Surgery
- Pre-operative chemotherapy
  - Surgery
  - Post-operative chemotherapy

Post-operative
- Surgery
- Post-operative chemotherapy
- Surgery
  - Post-operative Chemoradiation
Can we be more precise in peri-operative treatment for gastro-oesophageal cancer?

Multimodality treatment of OGJ/ gastric adenocarcinoma

Pre-operative chemotherapy

Surgery

Post-operative chemotherapy

Surgery
Acknowledgement

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