Current standards of care in gastric cancer

Prof Eric Van Cutsem, MD, PhD
Digestive Oncology
Leuven, Belgium
Eric.VanCutsem@uzleuven.be
Outline

❖ Resectable gastric cancer:
  ❑ the role of neoadjuvant and adjuvant treatment
    ✔ guidelines

❖ Metastatic gastric cancer
  ❑ Cytotoxic agents
  ❑ Targeted agents
  ❑ Immune Checkpoint inhibitors
    ✔ guidelines
Gastric Cancer

Staging (CT Chest/Abdo, EUS, Laparoscopy)

- **cT1m**
  - Endoscopic Resection

- **cT1sm/2 cN0**
  - Partial or total Gastrectomy

- **cT(2)/3/4 cNx**
  - Perioperative Chemotherapy + Gastrectomy

Other options:
- postoperative CT or CRT

GEJ adenocarcinoma: periooperative CT or preoperative CRT

EORTC Recommendations  Eur J Cancer 2012 Nov;48(16):2941-53
Peri-operative Chemotherapy

St. II + III
Stomach + Cardia + Dist. Eso

MAGIC

CTx → Surgery → CTx

Primary endpoint: survival

UK MAGIC 2006: Perioperative Chemotherapy

5-y-OS

36%

23%

Stomach Cancer 74%
EGJ Cancer 26%

FLOT-4 Study in gastric cancer, including GEJ cancer

- Gastric or EGJ cancer type I-III
- Medically and anatomically operable
- cT2-4/cN- any/cM0 or cT-jede/cN+/cM0

Stratification: ECOG (0 or 1 vs. 2), localization (GÖÜ Type I vs. Type II/III vs. Magen), age (< 60 vs. 60-69 vs. ≥70 years) and nodal status (cN+ vs. cN-).

23% had Siewert type I
33% had Siewert type II/III

FLOT: Docetaxel 50mg/m², d1; 5-FU 2600 mg/m², d1; Leucovorin 200 mg/m², d1; Oxaliplatin 85 mg/m², d1, q2w

ECF/ECX: Epirubicin 50 mg/m², d1; Cisplatin 60 mg/m², d1; 5-FU 200 mg/m² (or Capecitabin 1250 mg/m² p.o. in 2 doses d1-d21), q2w

Survival ECF/ECX versus FLOT

<table>
<thead>
<tr>
<th></th>
<th>ECF/ECX</th>
<th>FLOT</th>
</tr>
</thead>
<tbody>
<tr>
<td>mOS</td>
<td>35 mo</td>
<td>50 mos</td>
</tr>
<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>p=0.012 (log rank)</td>
</tr>
</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></td>
</tr>
<tr>
<td>45%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
*projected OS-rates

Median follow-up time: 43 months

# FLOT 4: Subgroup Analysis: overall survival

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Patients (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>HR</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>716 (100%)</td>
<td>0.769</td>
<td>0.121</td>
<td>0.0121</td>
</tr>
<tr>
<td>Gender</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>male</td>
<td>533 (74%)</td>
<td>0.760</td>
<td>0.9299</td>
<td></td>
</tr>
<tr>
<td>female</td>
<td>183 (26%)</td>
<td>0.800</td>
<td>0.9402</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 60</td>
<td>315 (44%)</td>
<td>0.770</td>
<td>0.797</td>
<td></td>
</tr>
<tr>
<td>60-69</td>
<td>229 (32%)</td>
<td>0.759</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;=70</td>
<td>172 (24%)</td>
<td>0.723</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG PS</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ECOG 0</td>
<td>500 (70%)</td>
<td>0.776</td>
<td>0.8080</td>
<td></td>
</tr>
<tr>
<td>ECOG 1/2</td>
<td>216 (30%)</td>
<td>0.736</td>
<td>0.3520</td>
<td></td>
</tr>
<tr>
<td>Localization of tumor</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AEG I</td>
<td>165 (23%)</td>
<td>0.604</td>
<td>0.935</td>
<td></td>
</tr>
<tr>
<td>AEG II/AEG III</td>
<td>233 (33%)</td>
<td>0.893</td>
<td>0.772</td>
<td></td>
</tr>
<tr>
<td>Stomach</td>
<td>318 (44%)</td>
<td>0.5787</td>
<td>0.4171</td>
<td></td>
</tr>
<tr>
<td>Histological type</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>61</td>
<td>0.852</td>
<td></td>
<td></td>
</tr>
<tr>
<td>diffuse</td>
<td>191 (29%)</td>
<td>0.746</td>
<td></td>
<td></td>
</tr>
<tr>
<td>non-diffuse</td>
<td>464 (71%)</td>
<td>0.4171</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lymph node involvement</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN-</td>
<td>147 (21%)</td>
<td>0.642</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cN+</td>
<td>569 (79%)</td>
<td>0.806</td>
<td></td>
<td></td>
</tr>
<tr>
<td>cT-stage</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>22</td>
<td>0.5821</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1/2</td>
<td>113 (16%)</td>
<td>0.661</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T3/4</td>
<td>581 (84%)</td>
<td>0.790</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Barret</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>11</td>
<td>0.3396</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>598 (85%)</td>
<td>0.809</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>107 (15%)</td>
<td>0.619</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Signet ring cells</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>missing</td>
<td>36</td>
<td>0.7459</td>
<td></td>
<td></td>
</tr>
<tr>
<td>no</td>
<td>479 (70%)</td>
<td>0.796</td>
<td></td>
<td></td>
</tr>
<tr>
<td>yes</td>
<td>201 (30%)</td>
<td>0.740</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

R0 resection rate: 85% (FLOT) versus 74% (ECF), p=0.02

Hazard ratio = 1.35

But:
D2 lymphadenectomy 10%
D1 lymphadenectomy 36%
D0 lymphadenectomy 54%

→ Significant survival advantage in sub-optimally resected patients
Radiotherapy and D1+/D2 Surgery - Trials

**CRITICS**  
(NL, Sweden)  
Stage Ib-IVa

- CTx (ECX) → Resection → Radio-CTx
- CTx (ECX) → Resection → CTx (ECX)

**TOPGEAR**  
(AUS, CAN, EU)  
Stage Ib-IVa

- Radio-CTx → Resection → CTx (ECX)
- CTx → Resection → CTx
CRITICS Study in resectable gastric cancer

Verheij M et al. ASCO 2016; abstract 4000

Overall Survival

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS (%)</td>
<td>40.8</td>
<td>40.9</td>
</tr>
<tr>
<td>Median OS (yrs)</td>
<td>3.5</td>
<td>3.3</td>
</tr>
</tbody>
</table>
Resectable Oesophageal Cancer
CROSS Study (including GEJ cancer)

Randomized Phase III study - Netherlands

✓ Resectable oesophageal adenocarcinoma or SCC
✓ Stage II or III: T2-3/N0-1/M0 (CT scan + EUS ± PET Scan)
✓ WHO PS 0-1, weight loss < 10%, T length < 8 cm
✓ Primary objective: Overall survival + QOL

Paclitaxel 50mg/m² + carboplatin AUC2 weekly x 5 wks + RT 41.4 Gy

6 wks
Surgery

Surgery

Van Hagen et al, NEJM 366(22): 2074-2084
Survival benefit for pre-operative CRT overall
Median OS was 49.4 months with CRT+ surgery vs 24 months for surgery alone (p = 0.003) ⇒ This is an effective treatment option

Van Hagen et al, NEJM 366(22): 2074-2084
The issues in treatment of GEJ adenocarcinoma

- R0 resection
- pCR
- N0 status
- Failure pattern
- Tumor downstaging
  - are linked to survival and favour
    - perioperative chemotherapy with FLOT
    - and
    - preoperative CRT (CROSS)

Both preoperative CT (FLOT) and CRT (CROSS) allow safe surgery, although morbidity/mortality after CRT are increased more
Postoperative Chemotherapy
Gastric Adenocarcinoma

Multiple Adjuvant Studies

St. II + III Stomach Cancer

RANDOM

Surgery

CTx

Surgery
GASTRIC METAANALYSIS: Overall Survival for adjuvant chemotherapy compared to surgery

<table>
<thead>
<tr>
<th>Events, No./Patients, No.</th>
<th>Any Chemotherapy</th>
<th>Surgery Alone</th>
<th>Hazard Ratio (95% CI)</th>
<th>Favora Chemotherapy</th>
<th>Favora Surgery Alone</th>
<th>Observed Events–Expected Events (Variance)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Monochemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oura et al.,19 1989</td>
<td>42/154</td>
<td>48/153</td>
<td>0.85 (0.64–1.12)</td>
<td></td>
<td></td>
<td>−5.4 (2.7)</td>
</tr>
<tr>
<td>Nakajima et al.,22 2007</td>
<td>18/95</td>
<td>30/95</td>
<td>0.51 (0.29–0.90)</td>
<td></td>
<td></td>
<td>−7.9 (1.7)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>60/159</td>
<td>78/158</td>
<td>0.60 (0.42–0.84)</td>
<td></td>
<td></td>
<td>−17.3 (8.5)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.44; P = .51$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polychemotherapies</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorouracil + Mitomycin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>C + Other Without Anthracyclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nakajima et al.,21 1984</td>
<td>102/156</td>
<td>52/72</td>
<td>0.77 (0.54–1.09)</td>
<td></td>
<td></td>
<td>−8.3 (81.1)</td>
</tr>
<tr>
<td>Nakajima et al.,21 1990</td>
<td>47/208</td>
<td>60/235</td>
<td>0.77 (0.53–1.12)</td>
<td></td>
<td></td>
<td>−7.0 (26.7)</td>
</tr>
<tr>
<td>Nashimoto et al.,21 2003</td>
<td>15/128</td>
<td>21/124</td>
<td>0.60 (0.31–1.18)</td>
<td></td>
<td></td>
<td>−4.3 (6.5)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>162/572</td>
<td>133/481</td>
<td>0.74 (0.58–0.95)</td>
<td></td>
<td></td>
<td>−19.7 (66.4)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 0.43; P = .81$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fluorouracil + Mitomycin C</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>+ Anthracyclines</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coombes et al.,24 1990</td>
<td>96/120</td>
<td>100/149</td>
<td>0.85 (0.64–1.12)</td>
<td></td>
<td></td>
<td>−7.9 (68.7)</td>
</tr>
<tr>
<td>Lise et al.,22 1995</td>
<td>98/152</td>
<td>99/154</td>
<td>0.85 (0.64–1.12)</td>
<td></td>
<td></td>
<td>−7.5 (66.6)</td>
</tr>
<tr>
<td>Macdonald et al.,22 1995</td>
<td>90/109</td>
<td>96/112</td>
<td>0.94 (0.71–1.26)</td>
<td></td>
<td></td>
<td>−2.7 (64.4)</td>
</tr>
<tr>
<td>Thavara et al.,27 1996</td>
<td>25/44</td>
<td>38/43</td>
<td>0.57 (0.35–0.85)</td>
<td></td>
<td></td>
<td>−8.7 (15.6)</td>
</tr>
<tr>
<td>Popiela et al.,25 2004</td>
<td>42/283</td>
<td>47/52</td>
<td>0.67 (0.44–1.04)</td>
<td></td>
<td></td>
<td>−8.0 (20.2)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>331/491</td>
<td>382/509</td>
<td>0.82 (0.71–0.95)</td>
<td></td>
<td></td>
<td>−34.6 (175.5)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 3.82; P = .43$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Douglass and Staiblern,22 1982</td>
<td>64/88</td>
<td>73/82</td>
<td>0.66 (0.47–0.92)</td>
<td></td>
<td></td>
<td>−13.7 (63.0)</td>
</tr>
<tr>
<td>Engstrom et al.,29 1985</td>
<td>70/91</td>
<td>72/90</td>
<td>0.94 (0.68–1.30)</td>
<td></td>
<td></td>
<td>−2.0 (66.0)</td>
</tr>
<tr>
<td>Knoke et al.,21 1991</td>
<td>51/63</td>
<td>50/64</td>
<td>1.04 (0.70–1.53)</td>
<td></td>
<td></td>
<td>0.9 (25.1)</td>
</tr>
<tr>
<td>Bajetta et al.,22 2002</td>
<td>67/135</td>
<td>69/136</td>
<td>0.98 (0.70–1.37)</td>
<td></td>
<td></td>
<td>−0.7 (24.0)</td>
</tr>
<tr>
<td>Bocche et al.,30 2005</td>
<td>76/133</td>
<td>90/138</td>
<td>0.82 (0.61–1.11)</td>
<td></td>
<td></td>
<td>−3.2 (42.1)</td>
</tr>
<tr>
<td>Nitti et al.,24 2006</td>
<td>60/109</td>
<td>56/109</td>
<td>0.80 (0.60–1.20)</td>
<td></td>
<td></td>
<td>−3.0 (26.2)</td>
</tr>
<tr>
<td>Nitti et al.,25 2006</td>
<td>63/89</td>
<td>64/87</td>
<td>1.05 (0.74–1.49)</td>
<td></td>
<td></td>
<td>1.6 (81.6)</td>
</tr>
<tr>
<td>Subtotal</td>
<td>447/702</td>
<td>473/709</td>
<td>0.99 (0.78–1.29)</td>
<td></td>
<td></td>
<td>−25.8 (226.0)</td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 5.10; P = .53$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td>1000/1924</td>
<td>1007/1957</td>
<td>0.82 (0.76–0.89)</td>
<td></td>
<td></td>
<td>−97.4 (603.3)</td>
</tr>
</tbody>
</table>

Heterogeneity: $\chi^2 = 0.09; P = .90$

Test for $4$ regimens’ heterogeneity: $\chi^2 = 5.59; P = .13$

Paoletti X… Van Cutsem E et al. The Gastric Group- JAMA, 2010
GASTRIC Group Meta-analysis

Figure 3. Overall Survival Estimate After Any Chemotherapy or Surgery Alone Truncated at 10 Years

6% difference at 5 years
HR = 0.82; p < 0.001

Paoletti X… Van Cutsem E et al. The Gastric Group- JAMA, 2010
Neo-adjuvant and adjuvant therapy for gastric cancer: different strategies

Post-operative Chemoradiotherapy (trend to perioperative CT in academic centers)

Peri-operative Chemotherapy TOF/FLOT (ECF- 5FU/cisplatin)

Postoperative CT

Post-operative Chemotherapy (S-1 or combination)

Adapted from Van Cutsem E et al; expert discussion Barcelona; Ann Oncol 2011
Summary: adjuvant & neoadjuvant treatment

✓ Perioperative chemotherapy is the EU standard of care for localized gastric cancer (N+ and/or T3-4 resectable); for GEJ adenocarcinoma (esp. Siewert type 1 and 2: preoperative CRT – CROSS regimen is also a standard of care)

✓ Perioperative chemotherapy comprises a platinum compound and a fluoropyrimidine, given for 8-9 weeks pre- and postop.
  ✓ Taxanes improve perioperative chemotherapy outcomes

✓ Studies on integration of radiotherapy are ongoing (now focus on neoadjuvant)
✓ Anti-HER2 treatment is under investigation
✓ Immunotherapy is under investigation
Cytotoxics in metastatic gastric cancer

❖ Fluoropyrimidines:
✓ IV 5-FU
✓ capecitabine
✓ S1

❖ Platinums
✓ oxaliplatin
✓ Cisplatin

❖ Taxanes:
✓ docetaxel
✓ Paclitaxel

❖ Topo-isomerase inhibitors
✓ Irinotecan

❖ Anthracyclines
✓ epirubicin

☐ 2 cytotoxics better than 1
☐ 3 cytotoxics versus 2?

☐ Backbone for targeted agents
Metastatic Gastric Cancer 1st line

- Oxaliplatin can substitute for Cisplatin
  Some advantages, especially in older patients


- Capecitabine or S-1 can substitute for i.v. 5-FU

  Ajani et al. *J Clin Oncol* 2010; 28: 1547-1553

- A third drug increases the efficacy but also toxicity
  Epirubucine was used a lot in UK and NL
  Docetaxel: 3-weekly DCF regimen toxic - modified DCF/DOF preferred

  Van Cutsem E et al. *J Clin Oncol* 2006; 24: 4991-7
Second line chemo (taxane or irinotecan) in gastric cancer: Survival

- Median OS: 5.3 months vs 3.8 months (hazard ratio, 0.657; 95% CI, 0.485 to 0.891; one-sided P = .007).

- Other studies reported similar results

Thus-Patience P et al, EJC 2011
Ford H et al, Lancet Oncology 2014
Therapy for metastatic gastric cancer: different strategies

- FOLFOX
- mDCF or DOF
- S-1/cisplatin (Japan)
- Xelox (Korea)
- CF/ XP
- FOLFOX
- mDCF or DOF
- ECF/EOX (UK, NL)
  (FOLFIRI (Fr))

HER 2 pos: trastuzumab in all regions
Impact on survival of cytotoxics in advanced gastric cancer

‘New’ targets in gastric cancer

- Cytotoxics: modest impact: median survival of doublets/triplets usually <12 mo
- New Targets
  - Her2: trastuzumab*
  - Angiogenesis: ramucirumab*
  - EGFR
  - mTOR
  - cMET
  - FGFR
  - PD/PDL**
  - CTLA4
  - Claudine
  - Stemcell: STAT3
  - MMP9
  - PARP
  - ….

*Validated: approved agents
**Positive phase 3 trial
ToGA study: Primary endpoint: OS in IHC 3+ and/or FISH+

Primary endpoint: OS in IHC 3+ and/or FISH+

Event

Time (months)

No. at risk

F: fluoropyrimidine; C: cisplatin; T: trastuzumab

Bang Y, Van Cutsem E et al Lancet 2010
ToGA study
OS in IHC2+/FISH+ or IHC3+
exploratory analysis

<table>
<thead>
<tr>
<th>Event</th>
<th>1.0</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.9</td>
<td></td>
</tr>
<tr>
<td>0.8</td>
<td></td>
</tr>
<tr>
<td>0.7</td>
<td></td>
</tr>
<tr>
<td>0.6</td>
<td></td>
</tr>
<tr>
<td>0.5</td>
<td></td>
</tr>
<tr>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>0.2</td>
<td></td>
</tr>
<tr>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>0.0</td>
<td></td>
</tr>
</tbody>
</table>

Time (months)

<table>
<thead>
<tr>
<th>Events</th>
<th>OS</th>
<th>HR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC + T</td>
<td>120</td>
<td>16.0</td>
<td>0.65</td>
</tr>
<tr>
<td>FC</td>
<td>136</td>
<td>11.8</td>
<td></td>
</tr>
</tbody>
</table>

Bang Y, Van Cutsem E et al Lancet 2010
Management of advanced GC

- HER2-
- HER2+

Cytotoxic chemotherapy

Anti-HER2 agent + Cytotoxic chemotherapy
HER2 testing in gastric cancer

**Figure 2: Testing algorithm for HER2 status in gastric and gastro-oesophageal-junction adenocarcinomas**

IHC - immunohistochemistry. FISH - fluorescence in-situ hybridisation.

Van Cutsem E et al, LANCET 2016
Anti-Angiogenic Approach

REGARD: BSC ± Ramucirumab in 2° line treatment of gastric cancer

Overall survival

Progression free survival

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Ramucirumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients/events</td>
<td>117/108</td>
<td>238/199</td>
</tr>
<tr>
<td>Median PFS, mos (95% CI)</td>
<td>1.3 (1.3, 1.4)</td>
<td>2.1 (1.5, 2.7)</td>
</tr>
<tr>
<td>12-week PFS, %</td>
<td>16</td>
<td>40</td>
</tr>
</tbody>
</table>

HR (95% CI) = 0.483 (0.376, 0.620)

Stratified log-rank p-value <.0001
REGARD:
Time to Deterioration in ECOG PS (≥2)

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median, mo</td>
<td>5.1</td>
<td>2.4</td>
</tr>
<tr>
<td>(95% CI)</td>
<td>(3.5, 8.7)</td>
<td>(1.9, 3.7)</td>
</tr>
</tbody>
</table>
RAINFRO: Paclitaxel ± Ramucirumab in 2° line treatment of gastric cancer

Overall survival

<table>
<thead>
<tr>
<th></th>
<th>RAM + Pac (N = 330)</th>
<th>PBO + Pac (N = 335)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Events</td>
<td>256</td>
<td>260</td>
</tr>
<tr>
<td>Median (months)</td>
<td>9.6 (8.5, 10.8)</td>
<td>7.4 (6.3, 8.4)</td>
</tr>
<tr>
<td>6-month OS</td>
<td>72%</td>
<td>57%</td>
</tr>
<tr>
<td>12-month OS</td>
<td>40%</td>
<td>30%</td>
</tr>
</tbody>
</table>

HR 0.807 (95% CI 0.678-0.962)
Standard Log rank p=0.017

Progression free survival

<table>
<thead>
<tr>
<th></th>
<th>RAM + PTX</th>
<th>PBO + PTX</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patients / Events</td>
<td>330 / 279</td>
<td>335 / 296</td>
</tr>
<tr>
<td>Median(mos)</td>
<td>4.40 (4.24, 5.32)</td>
<td>2.86 (2.79, 3.02)</td>
</tr>
<tr>
<td>6-Mo PFS</td>
<td>36%</td>
<td>17%</td>
</tr>
<tr>
<td>9-Mo PFS</td>
<td>22%</td>
<td>10%</td>
</tr>
</tbody>
</table>

HR 0.635 (95% CI 0.536-0.752)
Standard Log rank p=0.0001

# Second-Line Targeted Treatment of Gastric/GEJ adenocarcinoma

<table>
<thead>
<tr>
<th>Agent</th>
<th>Trial</th>
<th>Treatment</th>
<th>N (randomization ratio)</th>
<th>Endpoint</th>
<th>OS (mo) HR (95% CI), P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ramucirumab (anti–VEGFR-2)</td>
<td>Phase III REGARD</td>
<td>BSC ± ramucirumab</td>
<td>335 (2:1)</td>
<td>OS</td>
<td>OS: 5.2 vs 3.8</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR: 0.776 (0.603–0.998)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P = 0.0047)</td>
</tr>
<tr>
<td></td>
<td>Phase III RAINBOW</td>
<td>Paclitaxel ± ramucirumab</td>
<td>665 (1:1)</td>
<td>OS</td>
<td>OS: 9.6 vs 7.4</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>HR: 0.807 (0.678–0.962)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(P = 0.0169)</td>
</tr>
</tbody>
</table>

Progression: evaluation of ECOG performance status, efficacy and tolerability of first-line chemotherapy, patient preferences and the need for remission

- ECOG PS 0–1 need for remission ++: Paclitaxel + ramucirumab
- ECOG PS 0–2 need for remission +/-: Ramucirumab monotherapy or irinotecan monotherapy or taxane monotherapy
- ECOG PS 2–4 or patient preference: Active symptom control
Figure 2. T-cell Activation in Tumor Milieu.

Phase 3 ATTRACTION-2: Nivolumab for GC after standard treatment

Key eligibility criteria:
- Unresectable advanced or recurrent gastric or gastroesophageal junction cancer
- Refractory to/intolerant of ≥2 standard therapy regimens
- ECOG PS of 0 or 1

Randomization
2:1

Nivolumab
3 mg/kg IV Q2W

Stratification:
- Country (Japan vs South Korea vs Taiwan)
- ECOG PS (0 vs 1)
- Number of organs with metastases (<2 vs ≥2)

Placebo

Primary endpoint:
- OS

Secondary endpoints:
- Efficacy (PFS, BOR, ORR, TTR, DOR, DCR)
- Safety

Exploratory endpoint:
- PD-L1 tumor expression

Patients were permitted to continue treatment beyond initial RECIST v1.1–defined disease progression, as assessed by the investigator, if receiving clinical benefit and tolerating study drug.

Retrospective determination of tumor PD-L1 expression, defined as staining in ≥1% (or ≥5%) of tumor cells, was performed in a central laboratory using immunohistochemistry (28-8 pharmDx assay) for patients with available tumor samples.

BOR, best overall response; DCR, disease control rate; DOR, duration of response; ECOG PS, Eastern Cooperative Oncology Group performance status; IV, intravenous; ORR, objective response rate; PFS, progression-free survival; Q2W, every 2 weeks; RECIST, Response Evaluation Criteria In Solid Tumors; TTR, time to tumor response

Kang YK et al. Lancet 2017 Dec 2;390(10111):2461-2471
Phase 3 ATTRACTION-2: Nivolumab for GC after standard treatment

**Key Points:**
- **ORR**: 11%
- **Any tumor shrinkage**: 37%
- **Significant OS benefit in Asian pts** (MST+1.2ms, 1y OS 26.6%, HR 0.63)
- **Well tolerated in pretreated GC pts** (d/c by AE 7% same with placebo)

Response assessment per RECIST v1.1: First scan 9 weeks after cycle 1, then every 6 weeks for year 1 and every 9 weeks thereafter

Primary endpoints: Safety (all cohorts); ORR by central review per RECIST v1.1 (cohort 1: all patients and patients with PD-L1–positive expression); ORR by central review per RECIST v1.1 (cohort 3)

PD-L1 positive was defined as combined positive score (CPS) ≥1 (previously reported as and equivalent to CPS ≥1%), where

\[
\text{CPS} = \frac{\text{PD-L1–positive cells}}{\text{total number of tumor cells}} \times 100
\]

\[\text{PD-L1 IHC 22C3 pharmDx} \quad \text{(Agilent Technologies, Carpinteria, CA, USA).}\]

\[\text{Capecitabine was administered only in Japan.}\]
KEYNOTE-059: Pembrolizumab in refractory gastric cancer – cohort 1

Keynote-059 (n=259)
Objective response rate 11.6%
  MSI-high 4/7; 57.1%
  Non-MSI-high 15/167; 9.0%
Median duration of response 8.4 months

‘New’ targets in gastric cancer

- Cytotoxics: modest impact: median survival of doublets/triplets usually <12 mo

- New Targets
  - Her2: trastuzumab*
  - Angiogenesis: ramucirumab*
  - EGFR
  - mTOR
  - cMET
  - FGFR
  - PD/PDL**
  - CTLA4
  - Claudine
  - Stemcell: STAT3
  - MMP9
  - PARP
  - …..

*Validated: approved agents
**Positive phase 3 trial
Genetic typing of gastric cancers

CIN
Chromosomal instability

- Intestinal histology
- Aneuploidy
- RTK amplification
- TP53 mutations
- HER2, EGFR, MET

Genomically stable

- Diffuse histology, young age
- CDH1, RHOA mutations (mobility, adhesion)
  - Sensitivity to m-TOR inhibitors in vitro

EBV

- High EBV burden
- Extensive DNA hypermethylation

- Amplification of PD-L1/2
- PIK3CA mutations

MSI
Microsatellite unstable

- Older age, High MSI
- Elevated mutation rate
- Hypermethylation (MLH1)

CIN
- Intestinal histology
- TP53 mutation
- RTK-RAS activation

GS

- Diffuse histology
- CDH1, RHOA mutations
- CLDN19-ARHGAP fusion
- Cell adhesion

Lei et al Gastroenterology 2013;145:554-565


Lei et al Gastroenterology 2013;145:554-565
Gastric cancer is one of the leading causes of cancer-related death worldwide. Many patients have inoperable disease at diagnosis or have recurrent disease after resection with curative intent. Gastric cancer is separated anatomically into true gastric adenocarcinomas and gastro-oesophageal-junction adenocarcinomas, and histologically into diffuse and intestinal types. Gastric cancer should be treated by teams of experts from different disciplines. Surgery is the only curative treatment. For locally advanced disease, adjuvant or neoadjuvant therapy is usually implemented in combination with surgery. In metastatic disease, outcomes are poor, with median survival being around 1 year. Targeted therapies, such as trastuzumab, an antibody against HER2 (also known as ERBB2), and the VEGFR-2 antibody ramucirumab, have been introduced. In this Seminar, we present an update of the causes, classification, diagnosis, and treatment of gastric cancer.
20th World Congress on Gastrointestinal Cancer
20–23 June 2018 / Barcelona, Spain
www.worldgiciancer.com