Systemic treatment of early and advanced gastric cancer

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Clinical Session – Gastrointestinal Tumours

5th ESO-ESMO Eastern Europe and Balkan Region

Masterclass in Medical Oncology

15-20 June 2018, Belgrade, Serbia
Outline

Adjuvant / peri-operative tx
- Background
- Oesophageal and GOJ adenocarcinoma
- Gastric adenocarcinoma

Advanced / metastatic disease
- Optimal First-line Treatment
- Salvage / 2nd line Therapy
- Targeted Therapies
- Investigational Approaches
- Take home messages
## Meta-analysis
### Adjuvant Chemotherapy in gastric cancer

<table>
<thead>
<tr>
<th>Trial</th>
<th>Number of trials</th>
<th>Number of patients</th>
<th>HR for OS (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mari et al, 2000</td>
<td>20</td>
<td>3658</td>
<td>0.82 (0.75-0.89)</td>
</tr>
<tr>
<td>Zhao &amp; Fang, 2008</td>
<td>15</td>
<td>3212</td>
<td>0.90 (0.84-0.96)</td>
</tr>
<tr>
<td>Liu et al, 2008</td>
<td>19</td>
<td>4599</td>
<td>0.85 (0.80-0.90)</td>
</tr>
<tr>
<td>GASTRIC group, Paoletti, 2010</td>
<td>17</td>
<td>3838</td>
<td>0.82 (0.76-0.90)</td>
</tr>
</tbody>
</table>
GOJ adenocarcinoma

Siewert classification of GEJ adenocarcinoma
AJCC (7th edition) staging

<table>
<thead>
<tr>
<th>Type</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>Adenocarcinoma of the lower esophagus. Center within 1–5 cm above the GEJ</td>
</tr>
<tr>
<td>II</td>
<td>True carcinoma of the cardia at the GEJ. Center between 1 cm above and 2 cm below the GEJ</td>
</tr>
<tr>
<td>III</td>
<td>Subcardial carcinoma. Center between 2 cm and 5 cm below GEJ</td>
</tr>
</tbody>
</table>

Oesophageal, GOJ & Gastric adenocarcinoma – work up

- Proper staging required and multidisciplinary discussion
- Endoscopy – biopsy
- Blood tests (FBC, renal-liver function, CEA, CA19-9)
- CT with contrast chest-abdomen and ………
  - Laparoscopic staging
  - PET/CT
  - EUS
- Nutritional assessment (? PEG, NG or J-tube)
Management
Oesophageal and GOJ adenocarcinoma

Locoregional disease: stage I-III (T1-4, N1-3, M0)

- Stage I: T1 & low risk T2, N0 → Surgery (Ivor-Lewis), ??ER/Ablation
- T2-T4a, N+ → Surgery
  - Preop chemoRT (CROSS study)
  - Definitive chemoRT (if not fit or decline surgery)
  - Periop chemo (FLOT study)
- T4b → definitive chemoRT
Preop CRT + Surgery vs Surgery Alone for Esophageal or Junctional Cancer

Chemoradiotherapy followed by surgery compared with surgery alone (N = 368)

- Paclitaxel 50 mg/m² + carboplatin AUC 2 on Days 1, 8, 15, 22, and 29
- Concurrent radiotherapy: 41.4 Gy in 23 fractions of 1.8 Gy
- Surgery within 6 wks after completion of chemoradiotherapy

Preop CRT + Surgery vs Surgery Alone for Esophageal or Junctional Cancer: OS

- R0 resection increased from 69% w/surgery alone to 92%
- 5-yr OS: 47% vs 34% with surgery alone
  - Squamous HR: 0.453
  - Adeno HR: 0.732
- Pathologic CR with CRT + surgery
  - Squamous: 49%
  - Adenocarcinoma: 23%
- Considered a new standard of care

PERI-OPERATIVE ADJUVANT CHEMOTHERAPY

MAGIC TRIAL

503 pt

R

ECF x 3

Surgery

Surgery

ECF x 3

• Adeno of the stomach or lower third of the oesophagus
• Stage II or grater
• Suitable for curative resection

FNLCC-FFCD 9703

224 pt

R

CF x 2-3

Surgery

CF x 3-4

Surgery

Cunningham, NEJM 2006
Boige, Asco 2007
Two positive randomized trials

**MAGIC TRIAL**

Primary endpoint: Overall Survival

- **5-y OS: 23% vs 36%**

**FNLCC-FFCD 9703**

- **P=0.009**
- **HR = 0.75**
- **(0.60 - 0.93)**

- **P=0.021**
- **HR = 0.69**
- **(0.50 - 0.95)**
Figure 1. Gastric cancer treatment algorithm.
Peri-operative Chemotherapy alone
PERI-OPERATIVE ADJUVANT CHEMOTHERAPY

MAGIC TRIAL

503 pt

R

ECF x 3

Surgery

Surgery

ECF x 3

FNLCC-FFCD 9703

224 pt

R

CF x 2-3

Surgery

CF x 3-4

Surgery

• Adeno of the stomach or lower third of the oesophagus
• Stage II or grater
• Suitable for curative resection

Cunningham, NEJM 2006

Boige, Asco 2007
Post-operative treatment alone
1. INT 0116 - First study to show benefit of adjuvant therapy

**Post-operative Chemoradiation: SWOG 9008/Intergroup 0116 Trial**

- Resected stage Ib-IV (M0) gastric or OGJ adenocarcinoma n=556
  - ≤D1 resection 54%, D1 = 36%, D2 = 10%
- Randomised
- Observation n=275
- 5-FU/LV Chemoradiation (4500Gy) n=281

- Median OS: 27 v 36m
- **HR for death 1.35; p=0.006**

Highly selected population (All had R0 resection + recovered from surgery) yet only 64% completed Rx

Significant Rx related toxicity:
- 1% toxic death
- 73% grade 3/4 AEs

*Macdonald et al., NEJM 2001*
Updated Analysis of SWOG-Directed Intergroup Study 0116: A Phase III Trial of Adjuvant Radiochemotherapy Versus Observation After Curative Gastric Cancer Resection

A

Overall Survival (%)

<table>
<thead>
<tr>
<th></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

B

Relapse-Free Survival (%)

<table>
<thead>
<tr>
<th></th>
<th>n</th>
<th>Events</th>
<th>Median (months)</th>
</tr>
</thead>
<tbody>
<tr>
<td>FU + leucovorin + RT</td>
<td>282</td>
<td>211</td>
<td>27</td>
</tr>
<tr>
<td>Observation</td>
<td>277</td>
<td>237</td>
<td>19</td>
</tr>
</tbody>
</table>

P < .001

Smalley S R et al. JCO 2012;30:2327-2333
INT-0116
Extent of surgery

- D0: 54% effective
- D1: 36% effective
- D2: 10% No effect of CT-RT

- Useful only in suboptimal surgery?
ARTIST- Adjuvant chemoradiation therapy

Adenocarcinoma of the stomach, D2 dissection =458

XPx 6

XP x 2/ XRT/ XP x 2

XP- capecitabine 1,000 mg/m² twice daily on days 1 to 14; cisplatin 60 mg/m² on day 1 every 3 weeks

XRT -45 Gy of radiation at 1.8 Gy per day, 5 days per week, for 5 weeks with continuous capecitabine 825 mg/m² twice daily during radiotherapy

Lee et al, JCO Jan 2012
ARTIST study

Lee J et al. JCO 2012;30:268-273
ACTS-GC: Adjuvant S-1 vs observation
N=1059

Sasako M et al. JCO 2011;29:4387-4393
CLASSIC: Adjuvant XELOX vs Observation N=1035

- Primary endpoint: 3-yr DFS
  - All pts in trial Asian; phase III
- XELOX given for 8 cycles
- 3-yr DFS benefit maintained across subgroups: disease stage, age, nodal status
- Nearly twice as many patients in observation vs XELOX arm experienced disease recurrence
  - XELOX: 18.1%
  - Observation: 30.1%
- Trend toward prolonged OS with XELOX vs observation (median follow-up: 34.4 mos)
  - HR: 0.74 (95% CI: 0.53-1.03; P = 0.0775)

Bang et al, The Lancet, 379, 315 -21, Jan 2012
Gastric Cancer: Nagoya Is Not New York

John S. Macdonald, Aptium Oncology, Los Angeles, CA

See accompanying article on page 4387

Adenocarcinoma of the stomach and gastroesophageal junction is a major health problem worldwide, with more than 900,000 new cases reported yearly. In the United States, this disease occurs approximately 10,500 deaths yearly. This review is based on a comprehensive analysis of the literature released in the last 20 years.

In patients identified preoperatively as having resectable gastric cancer, pre- and postoperative cytotoxic chemotherapy, a strategy termed perioperative therapy, has been accepted as a standard of care on the basis of results from the Medical Research Council Adjuvant Gastric Infusional Chemotherapy (MAGIC) trial published in 2006 by Cunningham et al.6 Many studies of postoperative adjuvant chemotherapy have been carried out in the United States and western Europe. Patients with stages II-IV (M0) disease who have undergone gastrectomy benefit in disease-free and overall survival from postoperative chemoradiotherapy.7,8

Table 1. Five-Year Survival Rates

<table>
<thead>
<tr>
<th>Study</th>
<th>Surgery (%)</th>
<th>Chemoradiotherapy/Chemotherapy (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>INT0116</td>
<td>28</td>
<td>43</td>
</tr>
<tr>
<td>MAGIC</td>
<td>23</td>
<td>36</td>
</tr>
<tr>
<td>ACTS-GC</td>
<td>61</td>
<td>72</td>
</tr>
</tbody>
</table>

Table 2. Patient Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>INT0116</th>
<th>MAGIC</th>
<th>ACTS-GC</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>554</td>
<td>503</td>
<td>1,034</td>
</tr>
<tr>
<td>T3/T4, %</td>
<td>68</td>
<td>64</td>
<td>45</td>
</tr>
<tr>
<td>Node positive, %</td>
<td>85</td>
<td>72</td>
<td>89</td>
</tr>
</tbody>
</table>

Table 3. INT0116 5-Year Survival Estimates by T Stage and Nodal Status

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Chemoradiotherapy (%)</th>
<th>Surgery Only (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nodal status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>N0</td>
<td>60</td>
<td>44</td>
</tr>
<tr>
<td>N1-3</td>
<td>50</td>
<td>37</td>
</tr>
<tr>
<td>N &gt; 4</td>
<td>30</td>
<td>17</td>
</tr>
<tr>
<td>Stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>T1-2</td>
<td>56</td>
<td>38</td>
</tr>
<tr>
<td>T3</td>
<td>38</td>
<td>20</td>
</tr>
</tbody>
</table>

Abbreviations: ACTS-GC, Adjuvant Chemotherapy Trial of TS-1 for Gastric Cancer; INT0116, Intergroup 0116; MAGIC, Medical Research Council Adjuvant Gastric Infusional Chemotherapy.
A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study

Study objective
- To investigate the efficacy and safety of CRT vs CT following neo-adjuvant CT and surgery in patients with resectable GC

*3 cycles of ECC (epirubicin, cisplatin/oxaliplatin + capecitabine);
†45 Gy in 25 fractions + cisplatin q1w + capecitabine qd.

Cats A et al. Lancet Oncol May 2018
A multicenter randomized phase III trial of neo-adjuvant chemotherapy followed by surgery and chemotherapy or by surgery and chemoradiotherapy in resectable gastric cancer: First results from the CRITICS study

Key results
- Treatment completed: 46% with CT vs 55% with CRT
- After a median follow-up of 50 months, 405 patients had died

<table>
<thead>
<tr>
<th></th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>5-year OS, %</td>
<td>41.3</td>
<td>40.9</td>
</tr>
<tr>
<td>p-value</td>
<td>0.99</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade ≥3 AEs</th>
<th>CT</th>
<th>CRT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological, %</td>
<td>44</td>
<td>34</td>
</tr>
<tr>
<td>p-value</td>
<td>0.01</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal, %</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>p-value</td>
<td>0.14</td>
<td></td>
</tr>
</tbody>
</table>

Conclusion
- Only ~50% of patients completed the treatment
- No significant difference in OS was observed between postoperative CT vs CRT in patients with resectable GC

Cats A et al. Lancet Oncol May 2018
Adjuvant Therapy in Gastric Cancer Improves OS

- **Postoperative RT + chemotherapy (US)**[1]
  - Treatment: 5-FU/LV + RT (INT-0116 study)
    - 10% ↑ 5-yr OS; HR: 0.76

- **Preop and postop chemo (UK) without RT**[2]
  - Treatment: ECF (MAGIC study) (until ASCO 2017)
    - 13% ↑ 5-yr OS; HR: 0.75

- **Postop chemo (Asia): 2 trials, 2000 pts, D2 resection, no RT**
  - Treatment: S-1 (oral 5-FU) (ACTS-GC study)[3]
    - 10% ↑ 5-yr OS; HR: 0.67
  - Treatment: postop capecitabine/oxaliplatin (CLASSIC trial)[4]
    - 9% ↑ 5-yr OS; HR: 0.66

- Survival improvements with all approaches similar, modest

Effect of Neoadjuvant Chemotherapy Followed by Surgical Resection on Survival in Patients With Limited Metastatic Gastric or Gastroesophageal Junction Cancer
The AIO-FLOT3 Trial
Kaplan-Meier analysis of progression-free survival (A) and overall survival (B) in patients with resectable (arm A), limited metastatic (arm B), or extensive metastatic (arm C) disease as well as progression-free survival (C) and overall survival (D) in patients with limited metastatic disease (arm B) who underwent surgery and no surgery. Crosshatching indicates censored data.
Table 1. Median Overall Survival and Progression-Free Survival by Arm

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Survival</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median OS (95% CI), mo</td>
<td>Median PFS (95% CI), mo</td>
<td></td>
</tr>
<tr>
<td>Arm A</td>
<td>NA</td>
<td>NA</td>
<td></td>
</tr>
<tr>
<td>Arm B</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>All</td>
<td>22.9 (16.5-NA)</td>
<td>10.7 (8.0-16.5)</td>
<td></td>
</tr>
<tr>
<td>With surgery</td>
<td>31.3 (18.9-NA)</td>
<td>26.7 (9.1-NA)</td>
<td></td>
</tr>
<tr>
<td>Without surgery</td>
<td>15.9 (7.1-22.9)</td>
<td>8.4 (4.1-10.4)</td>
<td></td>
</tr>
<tr>
<td>Arm C</td>
<td>10.7 (9.1-12.8)</td>
<td>6.3 (5.0-7.6)</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: NA, not achieved; OS, overall survival; PFS, progression-free survival.

Table 2. Response Rates According to RECIST for Patients With Limited (Arm B) and Extensive (Arm C) Metastatic Disease

<table>
<thead>
<tr>
<th>Study Arm</th>
<th>Complete Response, No. (%) [95% CI]</th>
<th>Partial Response, No. (%) [95% CI]</th>
<th>Overall Response, Complete + Partial, No. (%) [95% CI]</th>
<th>Stable Disease, No. (%) [95% CI]</th>
<th>Progressive Disease/Not Evaluable, No. (%) [95% CI]</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arm B</td>
<td>All (n = 60)</td>
<td>6 (10.0) [4.3-20.5]</td>
<td>30 (50.0) [37.7-62.3]</td>
<td>36 (60.0) [47.4-71.4]</td>
<td>18 (30.0) [19.8-42.6]</td>
</tr>
<tr>
<td></td>
<td>With surgery (n = 36)</td>
<td>5 (13.9) [5.6-29.1]</td>
<td>15 (41.7) [27.1-57.8]</td>
<td>20 (55.6) [39.6-70.5]</td>
<td>14 (38.9) [24.8-55.2]</td>
</tr>
<tr>
<td></td>
<td>Without surgery (n = 24)</td>
<td>1 (4.2) [&lt;0.01-21.9]</td>
<td>15 (62.5) [42.6-78.9]</td>
<td>16 (66.7) [46.6-82.2]</td>
<td>4 (16.7) [6.1-36.5]</td>
</tr>
<tr>
<td>Arm C (n = 127)</td>
<td>5 (3.9) [1.5-9.1]</td>
<td>50 (39.4) [31.3-48.1]</td>
<td>55 (43.3) [35-52]</td>
<td>44 (34.6) [26.9-43.3]</td>
<td>23 (18.1) [12.3-25.8]</td>
</tr>
</tbody>
</table>

*Best response refers to the best response achieved as evaluated by comparison of baseline tumor assessment with all available, subsequent tumor assessments until surgical resection was conducted, if applicable. Tumor assessments performed after surgery were not relevant for response.

b P = .04 for the numbers of patients with overall response (complete + partial) in arm B compared with those in arm C, using 2-sided Fisher exact test. The P value is presented only if P < .05.
Take home message early gastric/GEJ adenocarcinoma(1)

- Surgery is part of the mainstay of treatment of locally advanced gastric cancer
- Pre-op chemoRT may be becoming the new gold standard for lower oesophageal / GOJ adenocarcinoma
- Peri-operative chemotherapy is still the gold standard for gastric adenocarcinoma (but FLOT > ECF)
Take home message (2)

- USA ➔ favors adjuvant CRT
- Western Europeans ➔ favor perioperative CT
- Asians ➔ favor adjuvant CT
Take home message (3)

- Proper staging
- Multidisciplinary approach
Treatment for advanced gastric cancer: What is standard of care?  
ESMO guidelines

Inoperable or metastatic

Surgery → Re-assess

Palliative chemotherapy

Best supportive care if unfit for treatment

- HER-2 negative
  - Platinum+ fluoropyrimidine-based doublet or triplet regimen

- HER-2 positive
  - Trastuzumab + CF/CX

Consider clinical trials of novel agents

2nd line chemo
Clinical trials if adequate PS

## REAL-2 Trial: Capecitabine vs 5-FU, Oxaliplatin vs Cisplatin

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dose/Details</th>
</tr>
</thead>
<tbody>
<tr>
<td>ECF (n = 249)</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td>50 mg/m² IV q3w</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>60 mg/m² IV q3w</td>
</tr>
<tr>
<td>5-FU</td>
<td>200 mg/m²/d IV given continuously</td>
</tr>
<tr>
<td>ECX (n = 241)</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td>50 mg/m² IV q3w</td>
</tr>
<tr>
<td>Cisplatin</td>
<td>60 mg/m² IV q3w</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>625 mg/m² PO BID continuously</td>
</tr>
<tr>
<td>EOF (n = 235)</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td>50 mg/m² IV q3w</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m² IV q3w</td>
</tr>
<tr>
<td>5-FU</td>
<td>200 mg/m²/d IV given continuously</td>
</tr>
<tr>
<td>EOX (n = 239)</td>
<td></td>
</tr>
<tr>
<td>Epirubicin</td>
<td>50 mg/m² IV q3w</td>
</tr>
<tr>
<td>Oxaliplatin</td>
<td>130 mg/m² IV q3w</td>
</tr>
<tr>
<td>Capecitabine</td>
<td>625 mg/m² PO BID continuously</td>
</tr>
</tbody>
</table>

- 2 x 2 randomization, 8 cycles
- Noninferiority of X over F and O over C with 1-yr survival of 35% (1-side α of 5%)

REAL 2: OS, 5-FU vs Capecitabine

![Graph showing survival probabilities for 5-FU and Capecitabine over years since randomization.]

Probability of Survival (%)

Yrs Since Randomization

Pts at Risk, n

<table>
<thead>
<tr>
<th></th>
<th>5-FU</th>
<th>Capecitabine</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>484</td>
<td>480</td>
</tr>
<tr>
<td>1</td>
<td>178</td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>37</td>
<td>52</td>
</tr>
<tr>
<td>3</td>
<td>8</td>
<td>12</td>
</tr>
</tbody>
</table>

REAL 2: OS, Cisplatin vs Oxaliplatin


<table>
<thead>
<tr>
<th>Yrs Since Randomization</th>
<th>Cisplatin</th>
<th>Oxaliplatin</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>187</td>
<td>474</td>
</tr>
<tr>
<td>2</td>
<td>41</td>
<td>198</td>
</tr>
<tr>
<td>3</td>
<td>10</td>
<td>48</td>
</tr>
</tbody>
</table>

Pts at Risk, n

- Cisplatin: 490 187 41 10
- Oxaliplatin: 474 198 48 10
Does Epirubicin Add Anything in Advanced GE Cancer? FOLFIRI vs ECX

- N = 416
  - 1/3 GEJ, 2/3 gastric
- ORR: 39% vs 38%
- Median PFS: 5.3 vs 5.8 mos
- Median OS: 9.5 vs 9.7 mos
- TTF, toxicity favored first-line FOLFIRI over ECX

Phase III ToGA: Trastuzumab + Chemo in Advanced HER2+ Gastric Cancer

- **Rationale:** a subpopulation of gastric cancers overexpress HER2

Stratified by ECOG PS, advanced vs metastatic, gastric vs GEJ, measurable disease, capecitabine vs 5-FU

- **Pts with**
  - advanced gastric cancer screened for HER2 status (N = 3803)
  - Pts with HER2+ advanced gastric cancer (n = 810; 22% of successful screenings)

- **Primary endpoint:** OS

  *Selected at investigator’s discretion: 5-FU 800 mg/m²/day infusional on Days 1-5 q3w x 6; capecitabine 1000 mg/m² BID on Days 1-14 q3w x 6.*

Phase III ToGA: OS

Survival Probability

Median OS, mos

<table>
<thead>
<tr>
<th>Events, n</th>
<th>Median OS, mos</th>
<th>HR</th>
<th>95% CI</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>FC + T 167</td>
<td>13.8</td>
<td>0.74</td>
<td>0.60-0.91</td>
<td>.0046</td>
</tr>
<tr>
<td>FC 182</td>
<td>11.1</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Pts at Risk, n

Mos

Phase III ToGA: OS in Pts With IHC 3+ or FISH+ and IHC 2+

Survival Probability

Mos

0 2 4 6 8 10 12 14 16 18 20 22 24 26 28 30 32 34 36

Pts at Risk, n

228 218 196 170 142 122 100 84 65 51 39 28 20 12 11 5 4 1 0

218 198 170 141 112 96 75 53 39 28 20 13 11 4 3 3 0 0 0

Exploratory analysis

Median Events, n

OS, mos

HR 95% CI

FC + T 120 16.0 0.65 0.51-0.83

FC 136 11.8

Survival Probability

Phase III Clinical Trials of HER2-Directed Therapy in Gastric Cancer

- **First line**
  - JACOB: capecitabine/cisplatin/trastuzumab ± pertuzumab (planned N = 780)[1]
    - Negative trial Tabernero et al ESMO 2017 abstr. 6160
  - HELOISE: capecitabine/cisplatin + 2 dose levels of trastuzumab (planned N = 400)[2]

- **Second line**
  - GATSBY: paclitaxel vs T-DM1 (N = 412)[3]
    - T-DM1 was no better than paclitaxel

2. ClinicalTrials.gov. NCT01450696.
Randomized Second-line Gastric Cancer Studies (2009-2013): Median OS

Improved OS in Phase III Trials of Second-line Chemo for Gastric Cancer

BSC ± Ramucirumab in Metastatic Gastric or GEJ Cancer ( REGARD): PFS, Response

<table>
<thead>
<tr>
<th></th>
<th>Ramucirumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts/events</td>
<td>238/199</td>
<td>117/108</td>
</tr>
<tr>
<td>Median, mos</td>
<td>2.1 (1.5-2.7)</td>
<td>1.3 (1.3-1.4)</td>
</tr>
<tr>
<td>(95% CI)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12-wk PFS, %</td>
<td>40</td>
<td>16</td>
</tr>
<tr>
<td>ORR, %</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>DCR, %</td>
<td>49</td>
<td>23</td>
</tr>
<tr>
<td>HR:</td>
<td>0.483 (95% CI: 0.376-0.620; P &lt; .0001)</td>
<td></td>
</tr>
</tbody>
</table>

BSC ± Ramucirumab in Metastatic Gastric or GEJ Cancer (REGARD): OS

Ramucirumab
Placebo

Pts/events 238/179 117/99
Median, mos 5.2 (4.4-5.7) 3.8 (2.8-4.7)
(95% CI)
6-mo OS, % 42 32
12-mo OS, % 18 11
HR: 0.776 (95% CI: 0.603-0.998; \( P = .0473 \))

2nd-Line Ramucirumab in Advanced Gastric Cancer (RAINBOW): OS

RAINBOW[1]

<table>
<thead>
<tr>
<th></th>
<th>Ram/Pac</th>
<th>Placebo/Pac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts/events, n</td>
<td>330/256</td>
<td>335/260</td>
</tr>
<tr>
<td>Median, mos (95% CI)</td>
<td>9.63 (8.48-10.81)</td>
<td>7.38 (6.31-8.38)</td>
</tr>
<tr>
<td>6-mo OS, %</td>
<td>72</td>
<td>57</td>
</tr>
<tr>
<td>12-mo OS, %</td>
<td>40</td>
<td>30</td>
</tr>
</tbody>
</table>

HR: 0.807 (95% CI: 0.678-0.962; P = .0169)

REGARD[2]

<table>
<thead>
<tr>
<th></th>
<th>Ram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts/events, n</td>
<td>238/199</td>
</tr>
<tr>
<td>Median, mos (95% CI)</td>
<td>5.2 (4.4-5.7)</td>
</tr>
<tr>
<td>6-mo OS, %</td>
<td>42</td>
</tr>
<tr>
<td>12-mo OS, %</td>
<td>18</td>
</tr>
</tbody>
</table>

Δ mOS = 2.3 mos

Second-line Ramucirumab in Adv Gastric Cancer (RAINBOW): PFS, Responses

RAINBOW[1]

<table>
<thead>
<tr>
<th></th>
<th>Ram/Pac</th>
<th>Placebo/Pac</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts/events, n</td>
<td>330/279</td>
<td>335/296</td>
</tr>
<tr>
<td>Median, mos (95% CI)</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>12-mo PFS, %</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>ORR, %</td>
<td>28</td>
<td>16</td>
</tr>
<tr>
<td>DCR, %</td>
<td>80</td>
<td>64</td>
</tr>
<tr>
<td>HR: 0.635 (95% CI: 0.536-0.752; P &lt; .0001)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

REGARD[2]

<table>
<thead>
<tr>
<th></th>
<th>Ram</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pts/events, n</td>
<td>238/199</td>
</tr>
<tr>
<td>Median, mos</td>
<td>2.1 (1.5-2.7)</td>
</tr>
<tr>
<td>6-mo PFS, %</td>
<td>3</td>
</tr>
<tr>
<td>12-mo PFS, %</td>
<td>49</td>
</tr>
<tr>
<td>ORR, %</td>
<td>3</td>
</tr>
<tr>
<td>DCR, %</td>
<td>49</td>
</tr>
</tbody>
</table>

RAINFALL: Capecitabine/5-FU + Cisplatin ± Ramucirumab in Metastatic Gastric CA

- Randomized, double-blind, phase III trial

- Primary endpoint: PFS

- Secondary endpoints: OS, PFS2, ORR, DCR, TTP, DoR, QoL, PK

Pts with metastatic gastric/GEJ CA with no prior first-line therapy (N = 616, planned)

- **Ramucirumab** 8 mg/kg IV Days 1, 8
- **Capecitabine** 1000 mg/m² PO Days 1-14
- **Cisplatin** 80 mg/m² IV Day 1

- **Placebo** IV Days 1, 8
- **Capecitabine** 1000 mg/m² PO Days 1-14
- **Cisplatin** 80 mg/m² IV Day 1

*Pts unable to take capecitabine receive 5-FU 800 mg/m²/day Days 1-5.

RAINFALL met the primary study endpoint by demonstrating a modest but significant increase in median PFS for ramucirumab plus chemotherapy versus placebo plus chemotherapy in the intent-to-treat population (5.85 vs. 5.55 months; HR 0.75, 95% CI [0.61, 0.94]; p = 0.011. Trends toward benefit with ramucirumab were seen across nearly every subgroup evaluated. ASCO GI January 19, 2018
VEGF Revisited?: Second and Later Line of Therapy

- **AVAGAST:** capecitabine/cisplatin ± bevacizumab\(^1\)
  - No OS benefit for addition of bevacizumab in first-line setting

- **Apatinib**
  - Small-molecule multitargeted TKI with activity against VEGFR
  - Phase III trial reported at ASCO 2014: median OS significantly longer with 850 mg QD vs placebo (195 vs 140 days, respectively; HR: 0.71)\(^2\)

Phase III Trials in Gastric Cancer: EGFR-Targeted Agents

- REAL3: ECX ± panitumumab (UK)\(^1\)
  - Negative: panitumumab had inferior outcomes
- EXPAND: capecitabine/cisplatin ± cetuximab (EU)\(^2\)
  - Negative: cetuximab trended inferior
- COG: BSC vs gefitinib (UK): negative\(^3\)

Trials conducted with no biomarker selection of pts
  - No biomarker identified in esophagogastrectomy cancer

cMET Antibodies in Gastric Cancer: Phase III Trials

RILOMET-1\[1\]
Locally advanced or metastatic gastric and AEG Cancer, MET-positive by immunohistochemistry (IHC) HER2 negative

Primary endpoint: OS in the Met IHC 2+/3+ pt subgroup

N = 450

ECX + Rilotumumab

1:1

ECX alone

R

Primary endpoint: OS

Both studies stopped prematurely

N = 800

ECX + Rilotumumab

1:1

ECX alone

Pembrolizumab in Gastric Cancer (KEYNOTE-012)

- Pembrolizumab therapy associated with PR in 13 of 39 pts by investigator review and 8 of 36 pts by central review
  - 53% of pts had decrease in lesion size
  - Median time to response: 8 wks
  - 4 of 8 responses ongoing at time of data cutoff
  - Median response duration: 40 wks (range: 20+ to 48+)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Investigator Review (n = 39)</th>
<th>Central Review (n = 36)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ORR, % (95% CI)</td>
<td>33 (19-50)</td>
<td>22 (10-39)</td>
</tr>
<tr>
<td>Best response, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CR</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>PR</td>
<td>13 (33)</td>
<td>8 (22)</td>
</tr>
<tr>
<td>SD</td>
<td>3 (8)</td>
<td>5 (14)</td>
</tr>
<tr>
<td>PD</td>
<td>23 (59)</td>
<td>19 (53)</td>
</tr>
<tr>
<td>No assessment</td>
<td>0</td>
<td>1 (3)</td>
</tr>
<tr>
<td>Not determined</td>
<td>0</td>
<td>3 (8)</td>
</tr>
</tbody>
</table>

Bang YJ, et al. ASCO 2015. Abstract 4001

Key results

**OS**

- Median OS, months (95%CI): 5.6 (4.3, 6.9)
- 12-month OS rate, %: 23.4

**PFS**

- Median PFS, months (95%CI): 2.0 (2.0, 2.1)

Conclusions

- In patients with advanced gastric or GEJ cancer progressing after ≥2 prior lines of therapy, pembrolizumab showed promising anti-tumour activity and durable responses.
- In patients with PD-L1-positive tumours, ORR was higher, but there were also responses observed in patients with PD-L1-negative tumours.
- Pembrolizumab was well tolerated.
- In patients with gastric or GEJ cancer who have progressed after ≥2 prior lines of therapy pembrolizumab may be a potential treatment option.

NIVOLUMAB (ONO-4538/BMS-936558) AS SALVAGE TREATMENT AFTER SECOND OR LATER-LINE CHEMOTHERAPY FOR ADVANCED GASTRIC OR GASTRO-ESOPHAGEAL JUNCTION CANCER (AGC): A DOUBLE-BLINDED, RANDOMIZED, PHASE III TRIAL

Key eligibility criteria:
- Age ≥ 20 years
- Unresectable advanced or recurrent gastric or gastroesophageal junction cancer
- Histologically confirmed adenocarcinoma
- Prior treatment with ≥ 2 regimens and refractory to/intolerant of standard therapy
- ECOG PS of 0 or 1

Primary endpoint:
- OS

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

Exploratory endpoint:
- Biomarkers

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.

Presented by Kang YK et al ASCO GI 2017
Hazard ratio, 0.63 (95% CI, 0.50–0.78)  
\( P < 0.0001 \)
### Kaplan-Meier Analysis

**Probability of Progression-Free Survival (%)**

<table>
<thead>
<tr>
<th>Time (months)</th>
<th>Nivolumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>330</td>
<td>163</td>
</tr>
<tr>
<td>2</td>
<td>131</td>
<td>41</td>
</tr>
<tr>
<td>4</td>
<td>83</td>
<td>17</td>
</tr>
<tr>
<td>6</td>
<td>46</td>
<td>9</td>
</tr>
<tr>
<td>8</td>
<td>31</td>
<td>7</td>
</tr>
<tr>
<td>10</td>
<td>19</td>
<td>4</td>
</tr>
<tr>
<td>12</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>14</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>16</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>18</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>20</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

**Median PFS [95% CI], months**

- **Nivolumab**: 1.61 [1.54–2.30]
- **Placebo**: 1.45 [1.45–1.54]

**12-Month PFS Rate [95% CI], %**

- **Nivolumab**: 7.6 [4.2–12.2]
- **Placebo**: 1.5 [0.3–4.8]

**Hazard ratio, 0.60 (95% CI, 0.49–0.75)**

*P < 0.0001*

---

*Presented by Kang YK et al. ASCO GI 2017*
<table>
<thead>
<tr>
<th></th>
<th>Nivolumab 3 mg/kg</th>
<th></th>
<th>Placebo</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 268)</td>
<td></td>
<td>(n = 131)</td>
<td></td>
</tr>
<tr>
<td>ORR, n (%)</td>
<td>30 (11.2)</td>
<td>[7.7–15.6]</td>
<td>0</td>
<td>[0–2.8]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>&lt; 0.0001</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BOR, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complete response</td>
<td>0</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Partial response</td>
<td>30 (11.2)</td>
<td></td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Stable disease</td>
<td>78 (29.1)</td>
<td></td>
<td>33 (25.2)</td>
<td></td>
</tr>
<tr>
<td>Progressive disease</td>
<td>124 (46.3)</td>
<td></td>
<td>79 (60.3)</td>
<td></td>
</tr>
<tr>
<td>DCR, n (%)</td>
<td>108 (40.3)</td>
<td>[34.4–46.4]</td>
<td>33 (25.2)</td>
<td>[18.0–33.5]</td>
</tr>
<tr>
<td>[95% CI]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td>0.0036</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median TTR (range), months</td>
<td>1.61 (1.4–7.0)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median DOR, months</td>
<td>9.53</td>
<td>[6.14–9.82]</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Presented by Kang YK et al. ASCO GI 2017
4014: Nivolumab ± ipilimumab in pts with advanced (adv)/metastatic chemotherapy-refractory (CTx-R) gastric (G), esophageal (E), or gastroesophageal junction (GEJ) cancer: CheckMate 032 study – Janjigian YY, et al

### Key results

#### OS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mOS, months (95%CI)</th>
<th>12-month OS rate, %</th>
<th>18-month OS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 3 mg/kg</td>
<td>6.2 (3.4, 12.4)</td>
<td>39</td>
<td>25</td>
</tr>
<tr>
<td>Nivolumab 1 mg/kg + ipilimumab 3 mg/kg</td>
<td>6.9 (3.7, 11.5)</td>
<td>35</td>
<td>28</td>
</tr>
<tr>
<td>Nivolumab 3 mg/kg + ipilimumab 1 mg/kg</td>
<td>4.8 (3.0, 8.4)</td>
<td>24</td>
<td>13</td>
</tr>
</tbody>
</table>

#### PFS

<table>
<thead>
<tr>
<th>Treatment</th>
<th>mPFS, months (95%CI)</th>
<th>6-month PFS rate, %</th>
<th>12-month PFS rate, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nivolumab 3 mg/kg</td>
<td>1.4 (1.2, 1.5)</td>
<td>17</td>
<td>8</td>
</tr>
<tr>
<td>Nivolumab 1 mg/kg + ipilimumab 3 mg/kg</td>
<td>1.4 (1.2, 3.8)</td>
<td>24</td>
<td>17</td>
</tr>
<tr>
<td>Nivolumab 3 mg/kg + ipilimumab 1 mg/kg</td>
<td>1.6 (1.4, 2.6)</td>
<td>12</td>
<td>10</td>
</tr>
</tbody>
</table>

Conclusions

- In patients with chemotherapy-refractory oesophagogastric cancer, nivolumab alone or in combination with ipilimumab demonstrated clinical activity irrespective of PD-L1 status
- Safety profile was consistent with previous findings
Take Home Messages

- Fluoropyrimidine + platinum agent (standard chemo): FOLFOX, CAPOX, capecitabine/cisplatin (anthracycline becoming less in favour)
- HER2+: trastuzumab added to first-line chemo
- Positive trials for VEGFR2 inhibitors as second-line therapy
  - Ramucirumab improves outcome alone and with paclitaxel
- Failed trials targeting EGFR, MET
- Immunotherapy trials ongoing; encouraging results. PDL1 expression data unclear
Thank you